

ARCHIVES OF SURGERY

EDITORIAL BOARD

CAPTAIN WALTMAN WALTERS, MC-V(S), U.S.N.R., Chairman

LESTER R. DRAGSTEDT, Chicago

EVARTS A. GRAHAM, St. Louis

ALFRED BLALOCK, Baltimore

ALTON OCHSNER, New Orleans

A. J. SCHOLL, Los Angeles

ARTHUR W. ALLEN, Boston

WILLIAM DARRACH, New York

WALTER E. DANDY, Baltimore

VOLUME 50
1945

PUBLISHERS
AMERICAN MEDICAL ASSOCIATION
CHICAGO, ILL.

CONTENTS OF VOLUME 50

JANUARY 1945. NUMBER 1

	PAGE
Orientation to the Mechanisms of Clinical Shock. E. A. Stead Jr., M.D., and J. V. Warren, M.D., Atlanta, Ga.....	1
Arteriovenous Fistula Between the Right Common Iliac Artery and the Inferior Vena Cava: Report of a Case of Its Occurrence Following an Operation for a Ruptured Intervertebral Disk with Cure by Operation. Robert R. Linton, M.D., and Paul D. White, M.D., Boston.....	6
Traumatic Hemothorax: Decortication in the Treatment of the Chronic Uninfected Type. Major Frank P. Coleman, Medical Corps, Army of the United States.....	14
Slipping of the Upper Femoral Epiphysis: Diagnostic and Therapeutic Considerations. William T. Green, M.D., Boston.....	19
Evaluation of Gelatin and Pectin Solutions as Substitutes for Plasma in the Treatment of Shock: Histologic Changes Produced in Human Beings. Captain Hans Popper and Lieutenant Bruno W. Volk, Medical Corps, Army of the United States; Karl A. Meyer, M.D., and Donald D. Kozoll, M.D., Chicago, and Lieutenant Commander Frederick Steigmann (MC), U.S.N.R.....	34
Malignant Renal Neoplasms: A Clinical and Pathologic Study. Benjamin S. Abeshouse, M.D., and Tobias Weinberg, M.D., Baltimore.....	46
Ligation of the Femoral Vein for Chronic Occlusive Arterial Disease: A Review of One Hundred and Eighteen Ligations. S. Thomas Glasser, M.D., New York.....	56

FEBRUARY 1945. NUMBER 2

Testicular Tumors. Major Vincent Vermooten, Medical Corps, Army of the United States.	63
Early Repair of Neural Wounds with Penicillin Therapy. Commander Nathan C. Norcross (MC), U.S.N.R.....	67
Convulsive Factor in Commercial Penicillin. A. Earl Walker, M.D., and Herbert C. Johnson, M.D., with the Technical Assistance of William H. Funderburk, B.S., Chicago	69
Ménière's Disease in a Deaf-Mute. Walter E. Dandy, M.D., Baltimore.....	74
Syndrome of Trauma to the Psoas Muscle. Major Elliott Michelson, Medical Corps, Army of the United States.....	77
Experience with Calculus of the Bladder in North China. Philip B. Price, M.D., Salt Lake City.....	82
Masked Traumatic Rupture of the Spleen. Joseph K. Narat, M.D., and Angelo L. Vincenti, M.D., Chicago, and Arthur F. Cipolla, M.D., Cicero, Ill.....	87

FEBRUARY—Continued

	PAGE
Progress in Orthopedic Surgery for 1943. A Review Prepared by an Editorial Board of the American Academy of Orthopaedic Surgeons (Concluded):	
XVIII. Amputations, Apparatus and Technic. Prepared by J. Warren White, M.D., Greenville, S. C.....	89
XIX. Research. Prepared by A. Steindler, M.D., and Staff, Iowa City.....	97
Preface	102
A Review of Urologic Surgery. Albert J. Scholl, M.D., Los Angeles; Frank Hinman, M.D., San Francisco; Alexander von Lichtenberg, M.D., México, D. F., Mexico; Alexander B. Hepler, M.D., Seattle; Robert Gutiérrez, M.D., New York; Commander Gershom J. Thompson (MC), U.S.N.R.; Edward N. Cook, M.D., Rochester, Minn.; Egon Wildbolz, M.D., Berne, Switzerland, and Vincent J. O'Connor, M.D., Chicago..	104

MARCH 1945. NUMBER 3

Chronic Thyroiditis and Primary Thyrotoxicosis (Exophthalmic Goiter). Kazim I. Gürkan, M.D., Istanbul, Turkey (Translated by Perihan Cambel, M.D.).....	125
Continuous Spinal Anesthesia: Observations on 1,200 Patients. R. C. Martin, M.D.; H. Livingstone, M.D., and V. Wellman, M.D., Chicago.....	130
Thromboplastic Reagent: Development of a More Suitable Preparation for Measuring Accelerated Clotting Tendency and for Use Following Administration of Dicoumarin (3,3'-Methylene-Bis-[4-Hydroxycoumarin]). Charles E. Brambel, Ph.D., Baltimore..	137
Transplantation of Epiphysial Cartilage. H. Leslie Wenger, M.D., New York.....	148
Blocking of the Middle Cervical and Stellate Ganglions with Descending Infiltration Anesthesia: Technic, Accidents and Therapeutic Indications. A. de Sousa Pereira, M.D., Oporto, Portugal.....	152
Protein Metabolism During Convalescence After Trauma: Recent Studies. John Eager Howard, M.D., Baltimore.....	166
Use of Omentum to Close Perforations of the Stomach. Philip B. Price, M.D., and Tunnie F. Lee, M.D., Salt Lake City.....	171
Cysts of the Urachus. C. F. Sawyer, M.D., Chicago.....	174

APRIL 1945. NUMBER 4

Prophylaxis of Wound Infection: Studies with Particular Reference to Soaps and Irrigation. L. W. Peterson, M.D., Chicago.....	177
Osseous, Cartilaginous and Mixed Tumors of the Human Breast: A Review of the Literature. Antonio Rottino, M.D., and Kathleen Willson, New York.....	184
Metabolic Alterations Following Thermal Burns: III. Effect of Variations in Food Intake on Nitrogen Balance of Burned Patients. John Winslow Hirshfeld, M.D.; William E. Abbott, M.D.; Matthew A. Pilling, M.D.; Carl G. Heller, M.D., Ph.D.; Frieda Meyer, Ph.D.; Harold H. Williams, Ph.D.; Allen J. Richards, B.S., and Robert Obi, A.B., Detroit.....	194
Influence of Environmental Temperature on Shock. H. C. Bergman, Ph.D., and Myron Prinzmetal, M.D., Los Angeles.....	201

APRIL—Continued

	PAGE
Blood Iodine Studies: VI. An Analysis of the Blood Iodine in Thyroid Disease. George M. Curtis, M.D., and M. Been Fertman, M.A., Columbus, Ohio.....	207
Early and Late Postoperative Ambulation: A Comparative study of Three Hundred and Three Cases. Vincente D'Ingianni, M.D., New Orleans.....	214
Topical Use of Concentrated Penicillin in Surface-Active Solution. Edwin J. Grace, M.D., Brooklyn, and Vernon Bryson, Ph.D., Cold Spring Harbor, N. Y.....	219

MAY 1945. NUMBER 5

Subtotal Gastrectomy. Erwin R. Schmidt, M.D., and Dermont W. Melick, M.D., Madison, Wis.	223
Postoperative Gouty Arthritis. Bernard J. Ficarra, M.D., and Ralph Adams, M.D., Boston	229
Acrylic Resin as an Implant for Correction of Facial Deformities. Kenneth W. Penhale, D.D.S., M.D., Chicago.....	233
Anomalous Fusion of the Scaphoid and the Greater Multangular Bone. Lieutenant Commander M. G. Henry (MC), U.S.N.R.....	240
Degenerative White Blood Cell Picture as an Indication of Toxemia from Burns. John Van Duyn II, M.D., Syracuse, N. Y.....	242
Congenital Malformations of the Anus and Rectum: A Clinical Study. Eugene T. Dmytryk, M.D., St. Louis.....	253
Acute Appendicitis in Childhood. H. William Scott Jr., M.D., and Paul F. Ware, M.D., Boston	258
Surgical Treatment of Lymphedema. J. L. Ransohoff, M.D., Cincinnati.....	269
Internal Derangements of the Knee Joint. Major Russell F. Jaekle, Medical Corps, Army of the United States.....	271

JUNE 1945. NUMBER 6

Some Recent Accomplishments of Thoracic Surgery. W. E. Adams, M.D., Chicago.....	277
Meckel's Diverticulum Containing Calculi. Arthur W. Allen, M.D., and Gordon A. Donaldson, M.D., Boston.....	286
Lymphosarcoma Primary in the Appendix: A Study of Twenty-Three Cases. Lieutenant (jg) Graham Knox (MC), U.S.N.R.....	288
Methods for Reducing Pain Following Hemorrhoidectomy: Technic and Results in Seventy-Two Cases. James C. Owings, M.D., Baltimore.....	293
Periarterial Infiltration in Diagnosis and Treatment of Migraine: Experimental and Clinical Experiences with Eucupine and Procaine Hydrochloride. Reynold Patzer, M.D.; Vincent Derbes, M.D., and Hugo Engelhardt, M.D., New Orleans.....	296
Pneumothorax Resulting from a Dissecting Gastric Ulcer: Review of the Literature and Report of a Case. Perry B. Hudson, M.D.; Lendall C. Gay, M.D., and Howard E. Newman, M.D., Washington, D. C.....	301

JUNE—*Continued*

	PAGE
Desmoid Tumor. Charles C. Green, M.D., Houston, Texas.....	304
An Unusual Ileoileal Intussusception. Milroy Paul, M.S. (Lond.), F.R.C.S. (Eng.), M.R.C.P. (Lond.), Colombo, Ceylon.....	307
Review of Urologic Surgery. Albert J. Scholl, M.D., Los Angeles; Frank Hinman, M.D., San Francisco; Alexander von Lichtenberg, M.D., México, D.F., Mexico; Alexander B. Hepler, M.D., Seattle; Robert Gutiérrez, M.D., New York; Com- mander Gershom J. Thompson (MC), U.S.N.R.; Edward N. Cook, M.D., Rochester, Minn.; Egon Wildbolz, M.D., Berne, Switzerland, and Vincent J. O'Connor, M.D., Chicago	309
General Index.....	335

ORIENTATION TO THE MECHANISMS OF CLINICAL SHOCK

E. A. STEAD JR., M.D.

AND

J. V. WARREN, M.D.

ATLANTA, GA.

To the uninitiated the literature on shock is confusing and difficult to understand. As used in the clinical literature of the last thirty years, the term shock has described a clinical picture characterized either by a sharp fall in arterial pressure or by the peripheral signs and symptoms of a decrease in cardiac output. When a physician said that a patient was in shock he was describing the general appearance of the patient. The term had no specific physiologic connotation. It did not indicate why the circulation had failed; it simply implied that it had failed.

From time to time various authors, including ourselves,¹ have attempted to restrict the use of the term shock to the circulatory insufficiency produced by a failure of venous return to the heart. Further work in the clinic has convinced us that a physician many times cannot determine at once the physiologic basis of the circulatory failure. He desires to describe in a word a clinical picture dominated by the peripheral signs and symptoms of circulatory insufficiency, without committing himself to the cause of the circulatory failure. By common use the word shock has become entrenched in this sense, and it does not seem wise or possible to attempt to change its meaning.

On theoretic grounds it is clear that the clinical picture called shock can be produced by failure of one of several portions of the circulation: first, by inability of the heart to pump the normal amount of blood because of weakness of the heart itself; second, by inability of the heart to fill properly because of pericardial tamponade; third, by

blocking of the main arterial paths, as in massive pulmonary embolus; fourth by inability of the heart to pump an adequate amount of blood, not because of weakness of the heart but because the venous inflow to the heart has failed; fifth, by generalized failure of cellular metabolism; sixth, by loss of normal vasoconstrictor tone.

SHOCK PRODUCED BY FAILURE OF THE HEART

An example of shock due to failure of the heart to pump blood is seen in a patient with a rapid heart rate resulting from paroxysmal auricular tachycardia, ventricular tachycardia or auricular flutter. Such a patient may demonstrate all of the classic signs and symptoms of shock. Indeed, when the patient is first seen it may not be at once apparent that poor cardiac action is the basis for the circulatory failure. The heart is not functioning efficiently as a pump because the diastole is too short to allow adequate filling of the heart. The clinician says that the patient is in shock because of the appearance of the patient; the physiologist says that the patient has circulatory insufficiency because of inadequate cardiac output. Slowing of the abnormal cardiac rate improves the patient and cures the shock.

Patients with recent massive myocardial infarctions involving the left ventricle may present the classic manifestations of shock.¹ Some authors have proposed other terms, such as "cardiac collapse,"² for this condition, while others use the simple descriptive term shock. The venous return to the heart is normal, but the heart is weakened so that it cannot maintain a normal output of blood. Increasing the venous pressure by transfusions or decreasing it by venesection has little effect on the patient's condition, because the primary disorder is in the heart itself.¹

In the terminal stages of cardiac failure, no matter what its cause, one may see evidences of

From the Medical Service of Grady Hospital and the Department of Medicine, Emory University School of Medicine.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Emory University School of Medicine.

1. Stead, E. A., Jr., and Eberl, R. V.: Shock Syndrome Produced by Failure of the Heart, *Arch. Int. Med.* 69:369-383 (March) 1942.

2. Harrison, T. R.: *Failure of the Circulation*, ed. 2. Baltimore, Williams & Wilkins Company, 1939.

shock superimposed on the manifestations of congestive heart failure. Here, just as in myocardial infarction, the heart itself is at fault, and the symptoms result from diminished cardiac output in the same fashion. A less common type of circulatory disturbance is that seen as the result of certain poisonings, such as acute phosphorus poisoning, in which there appears to be a severe degree of myocardial damage as a result of the direct action of the chemical.³

SHOCK CAUSED BY PERICARDIAL TAMPONADE

Acute pericardial tamponade resulting from a stab wound of the heart or from a rapidly forming pericardial effusion causes the typical picture of shock. Pallor, sweating, nausea and restlessness with a low arterial pressure, weak or absent radial pulse and cold extremities present a striking picture of acute circulatory failure. On close observation the venous pressure is found to be increased, but because the neck veins are not dilated, as is frequently the case in congestive failure, the elevated venous pressure may be overlooked. Circulatory impairment occurs because the elevated intrapericardial pressure prevents adequate venous return to the heart. In other words, shock occurs because of blocked inflow to the heart. If either the tamponade is reduced or the venous pressure is elevated, the circulation improves and the evidences of shock disappear.

SHOCK CAUSED BY MASSIVE PULMONARY EMBOLUS

Shock may be produced by blocking the flow of blood through the major arteries. Such a situation is seen in patients with massive pulmonary emboli. Small pulmonary emboli may also be associated with circulatory failure, but it is likely that the mechanism for this type of shock is more complex.

SHOCK PRODUCED BY LOSS OF BLOOD, PLASMA OR FLUID

The clinical picture of shock develops in patients with massive hemorrhage. That this circulatory failure is the result of a decrease in blood volume can be easily proved. Transfusions of blood or plasma restore the circulation to normal.

Hemorrhage may be of many types. It may be external, or it may be internal into body cavities or into tissues. It may be selective. When the capillaries are injured but are not completely broken asunder, as in chemical peritonitis following a ruptured ulcer, in burns or in certain types of crushing injuries, plasma may leak

through the injured vessels although the capillary walls still hold the red cells within the vascular bed. This type of selective hemorrhage (loss of plasma) can result in a small blood volume and circulatory failure. That the circulatory failure is produced by the small blood volume is demonstrated again by the immediate response to plasma or whole blood.

In continued vomiting, severe diarrhea or Addison's disease, sufficient electrolytes and water may be lost from the body to produce circulatory failure on the basis of a small blood volume. Administration of isotonic solution of sodium chloride will increase the blood volume and improve the circulation.

Various authors have attempted to distinguish between the mechanism of circulatory failure caused by external hemorrhage and that present in other forms of shock.⁴ This distinction seems unwarranted to physicians actually caring for patients. The similar response to an increase in the blood volume of a patient with simple hemorrhage and of a patient with more selective loss of fluid from the blood stream, such as occurs in dehydration or loss of plasma, convinces them that both types of circulatory failure result from a small blood volume. It is true, of course, that the blood tends to be diluted after a hemorrhage and concentrated after a burn, but these differences are the result of the type of fluid lost from the blood stream and are not indicative of a fundamental difference in the mechanism of circulatory failure.

SHOCK PRODUCED BY FAILURE OF CELLULAR METABOLISM

Patients with acute infectious diseases frequently present the clinical picture of shock before they die. Because the usual picture of congestive failure is absent and because the circulation does not improve with administration of digitalis, it is frequently stated that these patients have peripheral circulatory failure or shock and that the circulation has failed because of an inadequate venous return to the heart. Observations were made on a group of patients with the clinical picture of shock produced by acute infections.⁵ By staying constantly with all patients admitted to the hospital with an overwhelming infection we obtained data before and during the period of circulatory failure. When the course was unfavorable, the circulation failed.

4. Wiggers, C. J.: The Present Status of the Shock Problem, *Physiol. Rev.* 22:74-123 (Jan.) 1942. Blalock, A.: Principles of Surgical Care, Shock and Other Problems, St. Louis, C. V. Mosby Company, 1942.
5. Ebert, R. V., and Stead, E. A., Jr.: Circulatory Failure in Acute Infections, *J. Clin. Investigation* 20: 671-679 (Nov.) 1941.

3. Warren, J. V., and Stead, E. A., Jr.: Unpublished observations.

a patient became cold and pale and the pulse pressure narrowed. At this time the physician in charge usually made the diagnosis of peripheral circulatory failure or shock. Studies of the blood of such patients showed that the plasma volume was normal and that there was no evidence of hemoconcentration. The vasomotor centers were functioning normally, as evidenced by the fact that blocking the nerves to a cold extremity caused the extremity to become warmer. These studies eliminated decrease in blood volume or failure of the vasomotor centers as the cause of the circulatory failure. The possibility still existed that the shock might be caused by an inadequate venous return because of pooling of blood in dilated splanchnic veins. If the pooling of blood in dilated veins and a decrease in effective venous pressure in the right atrium were responsible for the circulatory failure, raising the venous pressure would improve the circulation. The venous pressure was therefore recorded by inserting a needle in the external jugular or the femoral vein. Plasma and blood were then given rapidly until the veins of the body were engorged and until the venous pressure was elevated. The circulation did not improve; this demonstrated that the circulatory failure was not caused by an inadequate venous return. The data suggested that the heart was at least in part at fault and that the circulation could not be restored to normal by raising the venous pressure. Other studies showed that none of the circulatory system was functioning normally. The infection had produced metabolic disturbances in cells throughout the body, and the cells were slowly dying. The circulatory failure was secondary to a general failure in metabolism. Treatment with transfusions and digitalis was useless. If the infection could be controlled, the circulation improved. If it could not be, the patient died.

This same picture of shock is not infrequently seen in the medical wards in patients with advanced hepatic destruction due to cirrhosis or metastases, in patients dying with prolonged congestive failure and in patients dying from uremia or malignant hypertension. It is observed in the surgical wards as a manifestation of the circulatory failure which occurs some days after a severe burn or postoperatively in patients who acquire an infection. Unless the underlying metabolic defect can be corrected the patient dies. Treatment directed toward increasing the filling pressure of the heart is without avail.

As pointed out previously, any marked decrease in blood volume, be it from loss of plasma because of local damage to capillaries, from burns, peritonitis or trauma, from loss of blood by hemorrhage or from loss of fluid by dehydra-

tion, will cause circulatory failure. This circulatory failure occurs in the presence of a heart which is capable of functioning normally. If the inadequate circulation persists for a sufficient length of time, the circulatory insufficiency is no longer readily reversed by transfusions, and in time the condition becomes completely irreversible.

This condition of irreversible shock has puzzled clinicians and physiologists alike. For a time it was believed that the capillaries throughout the body became more permeable because of the circulatory insufficiency and that the shock became irreversible because any fluid placed in the vascular bed immediately leaked out. This thesis seemed plausible because, with the knowledge that any injury to the capillaries by trauma, burns or chemicals would cause the capillaries in the injured part to become abnormally permeable to protein, it seemed logical that generalized circulatory failure might injure all of the capillaries throughout the body and cause the entire capillary bed, even at a distance from the injury, to leak protein freely. This view was supported by the observation that complete ischemia in a part did cause local damage to and increased permeability of capillaries.

Studies on patients with circulatory failure from trauma, burns and infection have shown that the capillaries distant to the point of injury do not become abnormally permeable to protein because of prolonged circulatory failure.⁶ Only the capillaries at the site of injury leak protein freely. The cells of the blood vessels seem to be tougher than the cells in certain other organs, particularly the brain. In generalized circulatory failure, the central nervous system becomes depressed and the respirations stop before the capillaries throughout the body are injured sufficiently to leak protein. Similar observations have been made on the effects of lack of oxygen on the permeability of capillaries. If the capillaries of a part are completely deprived of oxygen, damage to them results and the capillaries in the anoxic part leak protein freely. If an unanesthetized patient is studied, it is found that progressive oxygen unsaturation of the arterial blood causes serious derangement in cerebral function before there is a detectable alteration in the permeability of the capillaries throughout the body.

6. Stead, E. A., Jr., and Warren, J. V.: The Protein Content of the Extracellular Fluid in Normal Subjects After Venous Congestion and in Patients with Cardiac Failure, Anoxemia and Fever, *J. Clin. Investigation* 23:283-287 (March) 1944. Fine, J., and Seligman, A. M.: Traumatic Shock: VII. A Study of the Problem of the "Lost Plasma" in Hemorrhagic, Tourniquet, and Burn Shock by the Use of Radioactive Iodo-Plasma Protein, *ibid.* 23:720-730 (Sept.) 1944.

shock superimposed on the manifestations of congestive heart failure. Here, just as in myocardial infarction, the heart itself is at fault, and the symptoms result from diminished cardiac output in the same fashion. A less common type of circulatory disturbance is that seen as the result of certain poisonings, such as acute phosphorus poisoning, in which there appears to be a severe degree of myocardial damage as a result of the direct action of the chemical.³

SHOCK CAUSED BY PERICARDIAL TAMPONADE

Acute pericardial tamponade resulting from a stab wound of the heart or from a rapidly forming pericardial effusion causes the typical picture of shock. Pallor, sweating, nausea and restlessness with a low arterial pressure, weak or absent radial pulse and cold extremities present a striking picture of acute circulatory failure. On close observation the venous pressure is found to be increased, but because the neck veins are not dilated, as is frequently the case in congestive failure, the elevated venous pressure may be overlooked. Circulatory impairment occurs because the elevated intrapericardial pressure prevents adequate venous return to the heart. In other words, shock occurs because of blocked inflow to the heart. If either the tamponade is reduced or the venous pressure is elevated, the circulation improves and the evidences of shock disappear.

SHOCK CAUSED BY MASSIVE PULMONARY EMBOLUS

Shock may be produced by blocking the flow of blood through the major arteries. Such a situation is seen in patients with massive pulmonary emboli. Small pulmonary emboli may also be associated with circulatory failure, but it is likely that the mechanism for this type of shock is more complex.

SHOCK PRODUCED BY LOSS OF BLOOD, PLASMA OR FLUID

The clinical picture of shock develops in patients with massive hemorrhage. That this circulatory failure is the result of a decrease in blood volume can be easily proved. Transfusions of blood or plasma restore the circulation to normal.

Hemorrhage may be of many types. It may be external, or it may be internal into body cavities or into tissues. It may be selective. When the capillaries are injured but are not completely broken asunder, as in chemical peritonitis following a ruptured ulcer, in burns or in certain types of crushing injuries, plasma may leak

through the injured vessels although the capillary walls still hold the red cells within the vascular bed. This type of selective hemorrhage (loss plasma) can result in a small blood volume and circulatory failure. That the circulatory failure is produced by the small blood volume is demonstrated again by the immediate response to plasma or whole blood.

In continued vomiting, severe diarrhea or Addison's disease, sufficient electrolytes and water may be lost from the body to produce circulatory failure on the basis of a small blood volume. Administration of isotonic solution of sodium chloride will increase the blood volume and improve the circulation.

Various authors have attempted to distinguish between the mechanism of circulatory failure caused by external hemorrhage and that present in other forms of shock.⁴ This distinction seems unwarranted to physicians actually caring for patients. The similar response to an increase in the blood volume of a patient with simple hemorrhage and of a patient with more selective loss of fluid from the blood stream, such as occurs in dehydration or loss of plasma, convinces them that both types of circulatory failure result from a small blood volume. It is true, of course, that the blood tends to be diluted after a hemorrhage and concentrated after a burn, but these differences are the result of the type of fluid lost from the blood stream and are not indicative of a fundamental difference in the mechanism of circulatory failure.

SHOCK PRODUCED BY FAILURE OF CELLULAR METABOLISM

Patients with acute infectious diseases frequently present the clinical picture of shock before they die. Because the usual picture of congestive failure is absent and because the circulation does not improve with administration of digitalis, it is frequently stated that these patients have peripheral circulatory failure or shock and that the circulation has failed because of an inadequate venous return to the heart. Observations were made on a group of patients with the clinical picture of shock produced by acute infections.⁵ By staying constantly with all patients admitted to the hospital with an overwhelming infection we obtained data before and during the period of circulatory failure. When the course was unfavorable, the circulation failed

3. Warren, J. V., and Stead, E. A., Jr.: Unpublished observations.
4. Wiggers, C. J.: The Present Status of the Shock Problem, *Physiol. Rev.* 22:74-123 (Jan.) 1942. *Physiol. A.: Principles of Surgical Care, Shock and Related Problems*, St. Louis, C. V. Mosby Company, 1942.
5. Ebert, R. V., and Stead, E. A., Jr.: Circulatory Failure in Acute Infections, *J. Clin. Investigation* 6:671-679 (Nov.) 1941.

The patient became cold and pale and the pulse sure narrowed. At this time the physician in charge usually made the diagnosis of peripheral circulatory failure or shock. Studies of the blood of such patients showed that the plasma volume was normal and that there was no evidence of hemoconcentration. The vasomotor centers were functioning normally, as evidenced by the fact that blocking the nerves to a cold extremity caused the extremity to become warmer. These studies eliminated decrease in blood volume or failure of the vasomotor centers as the cause of the circulatory failure. The possibility still existed that the shock might be caused by an inadequate venous return because of pooling of blood in dilated splanchnic veins. If the pooling of blood in dilated veins and a decrease in effective venous pressure in the right atrium were responsible for the circulatory failure, raising the venous pressure would improve the circulation. The venous pressure was therefore recorded by inserting a needle in the sternal jugular or the femoral vein. Plasma and blood were then given rapidly until the veins of the body were engorged and until the venous pressure was elevated. The circulation did not improve; this demonstrated that the circulatory failure was not caused by an inadequate venous return. The data suggested that the heart was at least in part at fault and that the circulation could not be restored to normal by raising the venous pressure. Other studies showed that one of the circulatory system was functioning normally. The infection had produced metabolic disturbances in cells throughout the body, and the cells were slowly dying. The circulatory failure was secondary to a general failure in metabolism. Treatment with transfusions and digitalis was useless. If the infection could be controlled, the circulation improved. If it could not be, the patient died.

This same picture of shock is not infrequently seen in the medical wards in patients with advanced hepatic destruction due to cirrhosis or metastases, in patients dying with prolonged congestive failure and in patients dying from anemia or malignant hypertension. It is observed in the surgical wards as a manifestation of the circulatory failure which occurs some days after a severe burn or postoperatively in patients who acquire an infection. Unless the underlying metabolic defect can be corrected the patient dies. Treatment directed toward increasing the filling pressure of the heart is without avail.

As pointed out previously, any marked decrease in blood volume, be it from loss of plasma because of local damage to capillaries, from rns, peritonitis or trauma, from loss of blood hemorrhage or from loss of fluid by dehydra-

tion, will cause circulatory failure. This circulatory failure occurs in the presence of a heart which is capable of functioning normally. If the inadequate circulation persists for a sufficient length of time, the circulatory insufficiency is no longer readily reversed by transfusions, and in time the condition becomes completely irreversible.

This condition of irreversible shock has puzzled clinicians and physiologists alike. For a time it was believed that the capillaries throughout the body became more permeable because of the circulatory insufficiency and that the shock became irreversible because any fluid placed in the vascular bed immediately leaked out. This thesis seemed plausible because, with the knowledge that any injury to the capillaries by trauma, burns or chemicals would cause the capillaries in the injured part to become abnormally permeable to protein, it seemed logical that generalized circulatory failure might injure all of the capillaries throughout the body and cause the entire capillary bed, even at a distance from the injury, to leak protein freely. This view was supported by the observation that complete ischemia in a part did cause local damage to and increased permeability of capillaries.

Studies on patients with circulatory failure from trauma, burns and infection have shown that the capillaries distant to the point of injury do not become abnormally permeable to protein because of prolonged circulatory failure.⁶ Only the capillaries at the site of injury leak protein freely. The cells of the blood vessels seem to be tougher than the cells in certain other organs, particularly the brain. In generalized circulatory failure, the central nervous system becomes depressed and the respirations stop before the capillaries throughout the body are injured sufficiently to leak protein. Similar observations have been made on the effects of lack of oxygen on the permeability of capillaries. If the capillaries of a part are completely deprived of oxygen, damage to them results and the capillaries in the anoxic part leak protein freely. If an unanesthetized patient is studied, it is found that progressive oxygen unsaturation of the arterial blood causes serious derangement in cerebral function before there is a detectable alteration in the permeability of the capillaries throughout the body.

6. Stead, E. A., Jr., and Warren, J. V.: The Protein Content of the Extracellular Fluid in Normal Subjects After Venous Congestion and in Patients with Cardiac Failure, Anoxemia and Fever, *J. Clin. Investigation* **23**:283-287 (March) 1944. Fine, J., and Seligman, A. M.: Traumatic Shock: VII. A Study of the Problem of the "Lost Plasma" in Hemorrhagic, Tourniquet, and Burn Shock by the Use of Radioactive Iodo-Plasma Protein, *ibid.* **23**:720-730 (Sept.) 1944.

What, then, is the cause of irreversible shock? It appears to be caused by irreversible changes in the metabolism of cells throughout the body because of prolonged circulatory insufficiency. When the circulation is inadequate, none of the cells of the body functions normally. In time these metabolic disturbances become irreversible and the cells begin to die. At this time increasing the venous return to the heart and elevating the venous pressure do not restore the cardiac output to normal. Thus the cells of the heart are also affected, and this in part accounts for the circulatory failure. The situation is similar to circulatory failure caused by infection. In so-called irreversible shock, the cells of the body die because of abnormalities in metabolism produced by prolonged circulatory failure. In uncontrolled infections the cells die because the growth of bacteria has interfered with the enzyme systems of the cells. In neither condition will transfusions restore the circulation to normal.

The relationship between shock which responds to therapy and irreversible shock may be illustrated by a description of the clinical course of a patient with a perforated peptic ulcer.

The patient entered the hospital in shock twelve hours after the perforation. He was pale, sweating and mentally confused and had a low arterial pressure with a narrow pulse pressure. Examination of the blood showed severe hemoconcentration and striking decrease in the plasma volume and the quantity of circulating plasma protein. The circulation failed because the blood volume had decreased to so great an extent that the venous return to the heart was inadequate. The heart was capable of pumping blood, but it was not receiving the blood to pump. This was proved by giving a large infusion of plasma. As the plasma volume rose, the venous return to the heart increased and the circulation rapidly returned to normal. The patient was dramatically improved. The cause of the hemoconcentration and the decrease in the quantity of plasma in the blood stream was not difficult to find. The abdomen contained several liters of fluid which had a protein concentration of about 4 Gm. per hundred cubic centimeters. The chemical irritation caused by the leakage of gastric juice over the peritoneal cavity had altered the permeability of the capillaries, and plasma had leaked from the blood stream into the peritoneal cavity.

The patient was taken to the operating room, and the perforation in the gastrointestinal tract was closed. The condition of the patient remained good for twenty-four hours, but after this time evidence of generalized peritonitis was present and the course from then on was progressively downward. Transfusions of plasma were continued, but the circulation again failed. The patient was once more pale and cold, with a weak, thready pulse. At this time there was no hemoconcentration and the plasma volume was normal. Further transfusions were without value because the circulatory failure was now caused not by a decrease in blood volume but by alterations in cellular metabolism produced by the infection.

SHOCK PRODUCED BY CHANGES IN TONE OF THE SMALL BLOOD VESSELS

Acute circulatory collapse of reflex origin (primary shock or common faint), with or without loss of consciousness, produces the clinical picture of shock. If the circulatory collapse is of short duration and the sweating not excessive the extremities remain warm. If it is more prolonged, the extremities may become as cold as in any other form of failure of the circulation. When the patient is first seen it may be impossible to decide whether this is a benign state or whether the patient is in a critical condition from loss of blood, pericardial tamponade or acute heart failure.

Recently observations have been made on the state of the circulation during the acute circulatory collapse occurring in blood donors.⁷ In spite of the striking pallor and the low arterial pressure, the cardiac output is not decreased. The pressure in the right atrium is not lowered. The circulatory failure is caused by a sharp fall in peripheral resistance, presumably by arteriolar dilatation. It appears as if sensory stimuli from any efferent nerve or from the emotional control of thought may cause a sudden reflex arteriolar dilatation, which results in a sharp fall in the arterial pressure. If the donor is upright, loss of consciousness will occur if the low arterial pressure is inadequate to maintain the cerebral blood flow against the force of gravity. This type of collapse is benign with the person in the recumbent position, because the over-all blood flow in the tissues is not reduced.

The factors responsible for the circulatory failure which can be produced by motionless standing in normal subjects after the ingestion of sodium nitrite⁸ and in patients with acute infections and fatigue have never been completely determined. How much of the circulatory failure is caused by venous pooling in veins the tone of which has been decreased by disease or by drugs and how much is the result of arteriolar vasodilatation secondary to reflex stimuli induced by the upright position have never been

7. Barcroft, H.; Edholm, O. G.; McMichael, J. and Sharpey-Schafer, E. P.: Posthaemorrhagic Fainting: Study by Cardiac Output and Forearm Flow. *Lancet* 1:489-491 (April 15) 1944. Warren, J. V. Brannon, E. S.; Stead, E. A., Jr., and Merrill, J.: The Effect of Venesection and Pooling of Blood in the Extremities on the Atrial Pressure and Cardiac Output in Normal Subjects with Observations on Acute Circulatory Collapse in Three Instances. *J. Clin. Investigation*, to be published.

8. Weiss, S.; Wilkins, R. W., and Hagman, F. W.: The Nature of the Circulatory Collapse Induced by Sodium Nitrite. *J. Clin. Investigation* 16:73-84 (July) 1937.

monstrated. It is possible that both mechanisms are important.

A pronounced decrease in arterial pressure about other evidences of circulatory insufficiency is seen after acute bouts of fever produced by malaria or intravenous injection of shold vaccine.⁹ Occasionally this occurs in other diseases, such as pneumonia. It would appear that the infection causes a loss of arterio-tone and a lowering of arterial pressure. Quantitative studies on this condition are needed before definite conclusions can be drawn. Anaphylactic shock causes a distinct fall in arterial pressure and the clinical picture of shock.

It is not clear to what degree generalized interference with cellular metabolism or hemoconcentration due to damage to capillaries produces circulatory failure.

GENERAL COMMENT

For the sake of clarity of presentation, the various mechanisms which produce the clinical picture of shock have been described separately. In any given patient several of these disturbances may be present at the same time. Infection and a small blood volume frequently occur together. Patients who have lost blood from hemorrhage are prone to have reflex circulatory collapse.

9. Chasis, H.; Goldring, W., and Smith, H. W.: Reduction of Blood Pressure Associated with the Pyrogenic Reaction in Hypertensive Subjects, *J. Clin. Investigation* 21:369-376 (July) 1942.

SUMMARY AND CONCLUSIONS

Much of the literature on shock will become clearer if it is remembered that as used by the clinician the term shock has no physiologic connotations. It simply describes a clinical picture dominated by the peripheral symptoms and signs of circulatory failure, which may be produced by weakness of the heart itself, inability of the heart to fill because of pericardial tamponade, blockage of the great arterial pathways, diminished inflow due to insufficient blood volume, generalized failure in cellular metabolism or loss of normal vasoconstrictor tone.

Generalized failure in cellular metabolism is a frequent cause of the shock syndrome. Prolonged circulatory failure from hemorrhage, loss of plasma or dehydration can so damage the metabolic systems of the cells that recovery is not possible, even though the circulation is temporarily restored. This condition is described in the literature as irreversible shock. The products of bacterial growth may likewise cause either reversible or irreversible cellular damage and produce the clinical picture of shock. Circulatory failure secondary to a generalized disturbance in cellular metabolism also occurs in patients with severe burns after the first few days, in patients with severe hepatic damage and in patients with renal failure or prolonged congestive heart failure.

ARTERIOVENOUS FISTULA BETWEEN THE RIGHT COMMON ILIAC ARTERY AND THE INFERIOR VENA CAVA

REPORT OF A CASE OF ITS OCCURRENCE FOLLOWING AN OPERATION FOR
A RUPTURED INTERVERTEBRAL DISK WITH CURE BY OPERATION

ROBERT R. LINTON, M.D., AND PAUL D. WHITE, M.D.

BOSTON

Numerous cases of traumatic arteriovenous fistula in which cure was obtained by surgical measures have been recorded in the literature. The abnormal physiologic effects produced by this condition have been thoroughly studied and reported by Reid,¹ Holman,² Makins³ and Matas,⁴ to whose writings the reader may refer. Large fistulas involving the major arteries and veins when allowed to persist result in gradual cardiac hypertrophy, dilatation and finally failure, and if they are not corrected death results. The first symptom that may develop is gradually increasing dyspnea on exertion. This is a warning of impending cardiac decompensation that should not be ignored.

The diagnosis of an acquired arteriovenous fistula is not difficult in the majority of cases. In an extremity a pulsating expansile mass is found in the region of the fistula. The limb frequently enlarges and on its surface many large engorged pulsating veins are seen. A continuous bruit and thrill with systolic accentuation over the pulsating mass are pathognomonic of an arteriovenous fistula. An immediate drop in the pulse rate following occlusion of the fistula by direct pressure over it (Branham's bradycardiac reaction) is characteristic of the condition. This is a useful test to differentiate a fistula from a true aneurysm.

The purpose of this paper is to present a case of arteriovenous fistula between the right common iliac artery and the inferior vena cava following an operation for a ruptured intervertebral

disk. Injury to the blood vessels was not realized at the time of the operation on the disk and the diagnosis of the fistula was not made until eight months later, when the patient complained of increasing dyspnea on exertion.

REPORT OF A CASE

C. J. G., a draftsman, was admitted to the Massachusetts General Hospital, Baker Memorial, on October 30, 1943, complaining of shortness of breath on exertion.

Present Illness.—On Sept. 23, 1942 he had a ruptured intervertebral disk removed and a spinal fusion at another hospital for pain in the back and legs. After that operation he had not been completely well, and his pain was relieved. In January 1943 he returned to work. He noticed slight edema of the ankles in the evening, which disappeared by morning. He felt well until February, when he first noticed fatigue on the day's work. In March he noted moderate difficulty on walking fast or climbing stairs, which before did not bother him. He saw three physicians, all of whom diagnosed his condition as some type of cardiac disease. On March 15 he had several severe nosebleeds.

Past History.—His past history was essentially contributory; there was no history of rheumatic fever, chorea or tonsillitis. He had had no serious illness except severe pain in the back of five years' duration for which he had an intervertebral disk removed and a spinal fusion done.

Physical Examination.—Examination showed a well developed and nourished, alert, cooperative patient. Neck: The veins of his neck were distended and exhibited deep pulsations. Lungs: The breath sounds were normal, with no rales. Heart: The heart was enlarged to the left; the left border of dullness at the apex was 11 cm. from the midline in the fifth intercostal space. The apex impulse was forceful and 3 cm. beyond the midclavicular line. The heart sounds were of good quality with a systolic murmur at the apex and a precordial protodiastolic gallop rhythm. The pulmonary second sound was greatly accentuated. A diastolic murmur was heard. The pulse rate was 100 and the pulse was regular in type. The blood pressure was 140 systolic and 40 diastolic. Prior to the operation on the disk his blood pressure was 120 systolic and 80 diastolic and at the termination of the operation it was 110 systolic and 75 diastolic. Abdomen: Abdominal examination gave negative results except for a continuous thrill with systolic accentuation felt in the right lower region and in the lower portion of the abdomen below the umbilicus. Auscultation revealed a loud continuous bruit with systolic accentuation, which was audible over the entire abdomen and over the course of the vessels of the right lower extremity, but not over the

From the Departments of Surgery and Medicine, Massachusetts General Hospital.

1. Reid, M. R., and McGuire, J.: *Arteriovenous Aneurysms*, Ann. Surg. 108:643, 1938.

2. Holman, E.: *Arteriovenous Aneurysm*, New York, The Macmillan Company, 1937.

3. Makins, G. H.: *Gun Shot Injuries to the Blood Vessels*, New York, William Wood & Company, 1919.

4. Matas, R.: *Some Experiences and Observations in the Treatment of Arteriovenous Aneurysms by the Intrascapular Method of Suture (Endo-Aneurysmorrhaphy) with Special Reference to the Transvenous Route*, Ann. Surg. 71:403, 1920.

eft. The same bruit was heard over the lumbar and the lower thoracic portion of the spine. It was loudest over the lower lumbar region. Extremities: There were normal pulsations in all the peripheral arteries, including the dorsalis pedis and the posterior tibial arteries of both feet. The pulsations in the right leg were diminished as compared with those in the left.

Laboratory Studies.—The red blood cell count was 3,300,000, with a hemoglobin content of 12 Gm. per hundred cubic centimeters. The white cell count was 6,600. A smear showed 70 per cent polymorphonuclear cells, 24 per cent small lymphocytes, 4 per cent monocytes and 2 per cent eosinophils. The platelets were normal, and the red blood cells showed achromia with some variation in size and shape. The blood nonprotein nitrogen content was 38 mg. per hundred cubic centimeters. A Hinton test on the blood gave a negative reaction. The vital capacity was 2.9 liters, or 68 per cent of normal. Examination of the urine showed a specific gravity of 1.028, a moderate trace of albumin and no sugar or diacetic acid. The sediment showed occasional casts, 2 red blood cells and 4 white blood cells per high power field. An electrocardiogram showed normal rhythm, with a rate of 100, a PR interval of 0.2 second, upright T waves and a slight deviation of the axis to the left. It was considered within normal limits except for the slightly prolonged PR interval.

Röntgenographic Examination.—Examination of the chest by Dr. Laurence L. Robbins showed a prominence of vascular shadows, particularly in the hilar region. The pulmonary fields were otherwise clear. The heart showed generalized enlargement, which was more marked in the region of the left ventricle. The measurements were 16.6 by 30.0 cm. The left auricle was not dilated. The pulsations of the heart, observed fluoroscopically, were not of the Corrigan type, but there was a wavelike character to the pulsations of both the aorta and the heart, which was similar to that of the venous pulsations in the engorged veins. There was definite evidence of pulsations in the liver. Examination of the lumbar portion of the spine showed no evidence of erosion. The spinous processes of the fourth and fifth lumbar vertebrae were partially resected, and there was narrowing of the fourth lumbar disk space.

Diagnosis.—A diagnosis of traumatic arteriovenous fistula between the right common iliac artery and the inferior vena cava was made.

Course.—The patient was digitalized.

First Operation.—On May 8, 1943, with the patient under ether anesthesia administered by the endotracheal route, through a right flank incision the first, second, third and possibly fourth lumbar ganglions were removed. There was a great deal of thickening and fibrosis, so that isolation of the ganglions was a little more difficult than usual. The vena cava was visualized, and it also seemed considerably thickened and surrounded with some scar tissue. A continuous thrill was palpable in it. There was no excessive bleeding or large venous vessels other than normal in this location. The wound was closed in layers. Cotton ligatures and sutures were used throughout.

The patient made a good postoperative recovery. The right foot and leg were dry and warm throughout, as compared with the left leg and foot, which were cool and moist. On May 18 a Miller-Abbott tube was passed and advanced into the small intestines to deflate them.

Second Operation.—On May 19, 1943, with the patient under ether anesthesia administered by the endotracheal route, the abdomen was opened through a right paramedian incision. The abdominal contents were normal except for pulsations in the liver. The bifurcation of the aorta and that of the vena cava were exposed by opening the posterior portion of the peritoneum over them. A pronounced continuous thrill with systolic accentuation was palpable over both these vessels and extending down through the right iliac vessels. It could be obliterated by finger point compression over the proximal end of the right common iliac artery. The fistula lay opposite the intervertebral space between the bodies of the fourth and fifth lumbar vertebrae. The aorta was first dissected free. It was surrounded with considerable scar tissue. A tourniquet clamp was placed around it. The left and the right common iliac artery were isolated and similar clamps placed around them. It was then possible to place another tourniquet clamp around the right common iliac artery just proximal to the fistula (fig. 1). Next an attempt was made to dissect free the right common iliac vein, which was enormously dilated, but because of scar tissue dissection was difficult, and a hole was torn in the vein. There was considerable loss of blood at the time, but by occluding the aortic tourniquet and the distal one around the right common iliac artery the bleed-

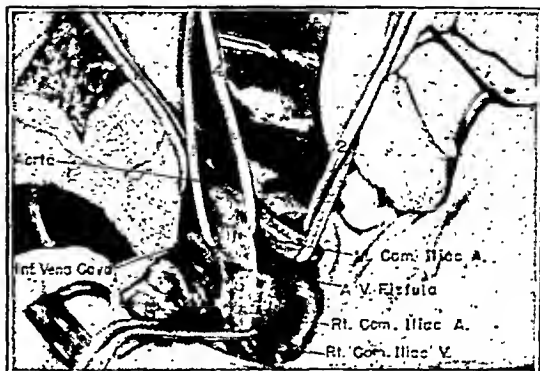


Fig. 1.—A retouched photograph showing the transperitoneal exposure of the bifurcation of the aorta and of the inferior vena cava. The site of the arteriovenous fistula, between the right common iliac artery and the inferior vena cava, is shown. The numbers 1, 2, 3 and 4 designate the location of the tourniquet clamps and the order in which they were applied. The arterial inflow was controlled first by application of the first tourniquet around the aorta. The arterial inflow from the collateral circulation was controlled next by applying the second and the third clamp, respectively, around the left common iliac artery and the right common iliac artery distal to the fistula. Finally the fourth tourniquet was applied to the right common iliac artery proximal to the fistula, thereby isolating the portion of that artery which contained the fistula. Note the huge size of the inferior vena cava and the right common iliac vein and the so-called venafication¹ of the right common iliac artery.

ing was readily controlled with a little pressure. An attempt was then made to free the left common iliac vein, but this was impossible also, because it was so adherent to the scar tissue. Finally it was decided that therapeutic venous occlusion could be obtained by interrupting the right external iliac vein. It was ligated in continuity just distal to its junction with the hypogastric vein. The right common iliac artery was doubly ligated distal to the bifurcation of the aorta

and proximal to the fistula. It was then divided, and an additional stitch ligature of cotton was placed distal to the silk ligature. The right common iliac artery was similarly treated distal to the fistula. Fortunately, it was possible to do this just proximal to its bifurcation, so that the hypogastric artery was not disturbed. The tear which had been made in the huge right common iliac vein was then closed with a running suture. The portion of the right common iliac artery containing the fistula was left attached to the inferior vena cava (fig. 2). It was felt unnecessary to resect it, since it had no tributaries which might if present have led to a recurrence. A definite arterial pulsation was noted in the distal ligated end of the right common iliac artery, indicating an excellent collateral arterial blood supply. The posterior portion of the peritoneum was closed with a running suture of no. 000 chromic catgut. The abdominal wound was closed in layers without drainage.

The operation required three and one-half hours. During the operation and in the immediate postoperative period he received 1,000 cc. of citrated blood. This was given because his blood pressure fell to 90 systolic and 60 diastolic near the termination of the operation. His pulse dropped from 120 beats per minute to 70 im-

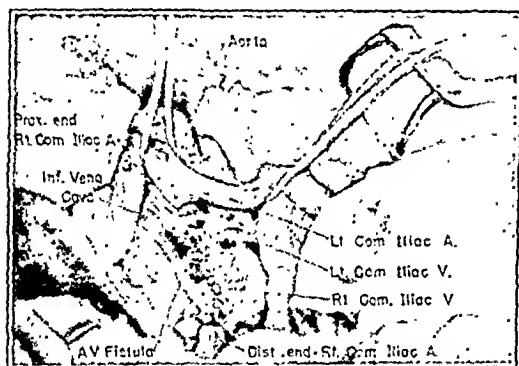


Fig. 2.—A retouched photograph to show the arrangement of the vessels at the completion of the operation. The right common iliac artery was divided and ligated both proximal and distal to the fistula. The portion of the artery containing the fistula was left attached to the inferior vena cava after ligation of both ends. Note the normal size of the ligated distal end of the right common iliac artery, with pulsations, indicating an adequate collateral arterial blood supply. The next step in the operation was closure of the posterior portion of the peritoneum over these vessels.

mediately after the proximal and the distal ligation of the right common iliac artery, which eradicated the fistula (fig. 3).

Postoperative Course.—Heparin was given by the continuous intravenous drip method for forty-eight hours, the clotting time being maintained between twenty and thirty-five minutes. Administration was stopped after that time, because it was obvious that the circulation of his right lower extremity was adequate.

On May 22, the third postoperative day, pulsations were first noted in the right dorsalis pedis and posterior tibial arteries. They were also present in the right femoral and popliteal arteries. The pulse in these vessels was not of the same caliber as that of the pulse in the vessels of the left leg. The blood pressure in the right arm was 148 systolic and 80 diastolic; in the left leg it was 180 systolic and 80

diastolic and in the right leg 110 systolic; no diastolic sound could be heard in the right leg.

On May 25 the patient complained of heaviness in his right thigh, and examination showed tenderness in the right groin extending down Hunter's canal. There was no pain in the calf; the whole leg was a little swollen and bluish. A diagnosis of thrombosis in the iliac and the femoral vein was made, and treatment with dicoumarin (3,3'-methylenebis [4-hydroxycoumarin]) was started. He received one dose of 300 mg. and two days an additional 100 mg. The prothrombin clotting time remained in the neighborhood of sixty seconds following administration of this drug; hence its use was discontinued. As the prothrombin time was still prolonged on June 1, he was given 3.2 mg. of menadiol bisulfite intramuscularly.

On May 27 another roentgenogram of the chest taken by Dr. Robbins, showed distinct improvement in the appearance of the heart and pulmonary fields. The pulmonary vascular congestion had completely disappeared. The heart was much smaller, with a transverse diameter of 14.6 by 28.3 cm. It was still slightly enlarged, however, the normal size for a patient of his height and weight being 12.5 cm.

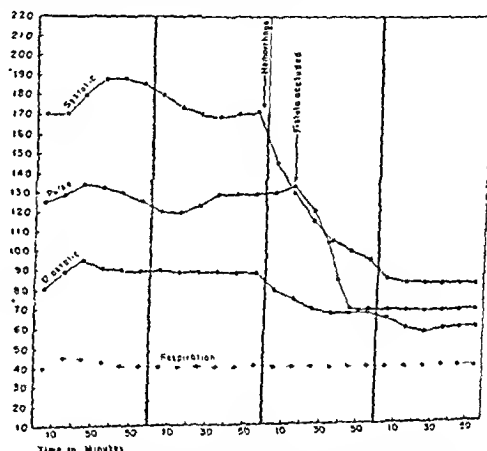


Fig. 3.—A reproduction of the anesthesia chart, showing the pulse and respiratory rates and the blood pressure during the operation. Note the fall in the blood pressure following the hemorrhage which occurred at the time the right common iliac vein was inadvertently torn and also the decided drop in the pulse rate (Brannan's bradycardiac reaction) which was observed when the fistula was eradicated.

On June 6 the patient was up, walking and anxious to go home. His general condition seemed good, and the circulation of his leg was adequate; so he was discharged from the hospital on this day.

After the patient's discharge from the Massachusetts General Hospital, Baker Memorial, he began raising foul-smelling sputum and had a low grade fever. On June 16 he was admitted to the New Haven Hospital (New Haven, Conn.), under the care of Dr. Gustaf E. Lindskog. A roentgenogram showed a large encapsulated pyopneumothorax on the left side of the chest between the lower and the middle lobe. It was felt that the origin of the empyema was secondary to a septic pulmonary infarction. The origin of the thrombus, which produced the infarction, was probably at the site of the arteriovenous fistula, where the rent in the right common iliac vein had to be sutured.

fatal pulmonary embolism probably had been prevented by interruption of the external iliac vein at the time of the operation.

On Aug. 18, 1944 the patient returned for a check-up. He stated that he was feeling well except that he had some cramps in the calf of his right leg at night. He also noticed that if he walked several miles his right leg seemed to tire more easily than his left, but he did not suffer severe intermittent claudication. He stated that he had been inducted into the Army of the United States but had been discharged because he was over 28 years of age and not because of the condition of his right leg. Physical examination at this time showed a normal-sized heart with a blood pressure of 120 systolic and 90 diastolic. Oscillations in his right calf, measured with a Tycos sphygmomanometer, were 1 mm. at 120 mm. of pressure, and in his left calf they were 3 mm. There was no atrophy of the right lower extremity, as measurements of the two legs were the same. There still were palpable pulsations in the right femoral, popliteal, dorsalis pedis and posterior tibial arteries.

Other Studies on the Circulation.—The pressure in the left antecubital vein before operation was 180 mm. of water above the right auricle; after operation it was 150 mm. The circulation time, as determined in the antecubital vein from the arm to the tongue preoperatively with calcium gluconate, was twenty seconds, and with ether from the arm to the lung it was eight seconds; postoperatively with calcium gluconate from the arm to the tongue it was twelve seconds, and with ether from the arm to the lung it was four seconds.

COMMENT

This case demonstrates a number of interesting points, which justifies its publication. It reveals that surgical removal of a ruptured intervertebral disk is not without danger to the great vessels which lie on the anterior surface of the bodies of the lumbar vertebrae, and it demonstrates that the common iliac artery can be interrupted without endangering the viability of the limb. Anatomic study of this region shows that the inferior vena cava is formed by the union of the two common iliac veins to the right of the median plane in front of the body of the fifth lumbar vertebra and behind the right common iliac artery. The latter crosses the distal end of the vena cava opposite the fourth intervertebral disk from right to left, and owing to the greater turgidity of the artery it fixes the vena cava to a certain extent against the vertebral column. As a result of this anatomic arrangement of the right common iliac artery, the inferior vena cava and the fourth intervertebral space, a sharp curet or instrument, such as is used for removal of a ruptured intervertebral disk, may transfix the artery and vein if suddenly forced through the anterior longitudinal vertebral ligament (fig. 4). Although in this patient the surgeon did not recognize that his instrument had injured these vessels, there seems little doubt that the fistula was produced in this manner. According to

Mixer,⁵ Talmadge⁶ and Walker,⁷ similar lesions have been produced by other surgeons while they were performing operations for ruptured intervertebral disks.

It appears offhand that such a vascular lesion would result in severe uncontrollable hemorrhage. An analysis of the situation, however, reveals that the blood escaping from the common iliac artery will follow the path of least resistance. Since the venous pressure in the inferior vena cava is approximately zero, escaping arterial blood will naturally flow into the large venous reservoir of the caval system rather than extravasate into the prevertebral spaces against resistance of the tissues. There was undoubtedly some local extravasation, as evidenced by the abnormal fibrous tissue around the great

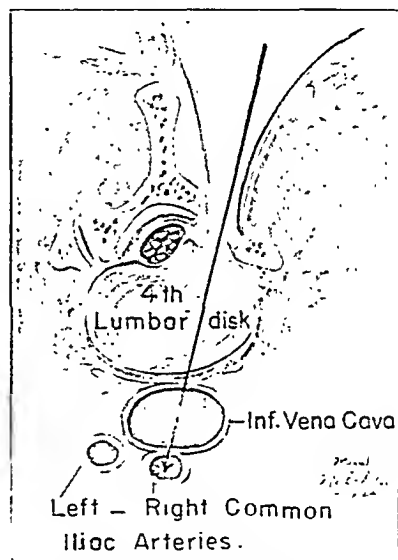


Fig. 4.—A diagrammatic drawing to show a cross section of the anatomic structure at the level of the fourth lumbar disk and the operative exposure to remove the ruptured disk. The arrow demonstrates the mechanism by which the fistula was produced. The curet transfixes the inferior vena cava and pierces the posterior wall of the right common iliac artery.

vessels found at operation, but it could not have been massive in the absence of shock following the operation.

The diagnosis of arteriovenous fistula was made in this case because of the beginning cardiac decompensation, the enlargement of the heart with a characteristic type of pulsation observed on fluoroscopic examination, and the

5. Mixer, W. J.: Personal communication to the authors.

6. Talmadge, S.: Personal communication to the authors.

7. Walker, A. E.: Personal communication to the authors.

continuous thrill with a systolic accentuation, which was heard loudest over the region of the lumbosacral articulation. The site of the fistula was localized preoperatively between the right common iliac artery and the inferior vena cava, because the thrill and the bruit were transmitted through the vessels of the right leg but not the left and the thrill was heard cephalad over the course of the inferior vena cava. Since the right common iliac artery crosses the distal end of the inferior vena cava from the left of the midline to the right side, it seemed most probable that the fistula was between these two vessels. The findings at operation proved this assumption to be correct.

In cases of this type, eradication of the arteriovenous fistula is the most important goal in the operative treatment, since the cardiovascular system will be restored to normal and thereby relieve the heart of the extra burden which it is carrying. Preservation of the circulation in the extremity is of second importance but none the less an objective to be attained. Therefore, the ideal to be achieved by surgical treatment is the accomplishment of both these aims. Eradication of the fistula in this case necessitated interruption of the right common iliac artery, thereby jeopardizing the circulation of the right lower extremity. According to the statistics of some authorities,⁸ the incidence of gangrene or other disturbances may be as high as 50 per cent following sudden ligation of the common iliac artery. Halsted,⁹ to the contrary, after a careful analysis of 30 reported cases of ligation of the common iliac artery, concluded that gangrene was likely to occur in about 6 per cent. He made the observation, however, that most of the patients who survived complained of severe cramps in the leg on walking a short distance. Fortunately, our patient's cardiac condition was not critical, so that it was possible first to safeguard the circulation of the leg without endangering seriously his life and later to eradicate the fistula.

The operative treatment was carried out, therefore, in two stages. The first was directed toward increasing the collateral blood supply of the extremity, so that when the common iliac artery was divided at the second stage the arterial circulation would be adequate to prevent ischemia

and gangrene. It consisted of a sympathectomy in which the first, second and third lumbar ganglia on the right side were removed. This produced maximum permanent vasodilatation of the right leg from the toes to the groin by inhibiting all the vasoconstrictor impulses from the central nervous system to the vascular system of the extremity. The importance of this cannot be overemphasized. The second stage was carried out ten days after the sympathectomy because it has been demonstrated by Smith¹⁰ that there is a temporary period of vasodilatation following the initial vasodilatation after division of the sympathetic ganglia. This is noticeable within forty-eight hours after sympathectomy, and the maximum permanent vasodilatation is not stabilized for five or six days longer. For this reason it is important to delay elective operations on major arteries until this stabilization after the sympathectomy has occurred.

The collateral circulation was further augmented at the second stage by therapeutic venous occlusion, since there is both experimental and clinical¹² evidence to prove that simultaneous ligation of the concomitant vein, when the main artery to a limb is ligated, will increase the flow of blood to the extremity and reduce the incidence of gangrene. Accordingly, in this case the external iliac vein was isolated and ligated in continuity. When exposed it was found to be of normal size, which indicated that most of the blood escaping through the fistula traveled directly through the tremendously enlarged vena cava to the heart. An additional reason for interrupting the external iliac vein was to prevent fatal pulmonary embolism, since trauma to the common iliac vein caused by the operative procedure might result in intravascular thrombosis. With the long venous channel to the thigh interrupted, the chance of a fatal pulmonary embolus was greatly reduced.

10. Smithwick, R. H.: Surgical Intervention on Sympathetic Nervous System for Peripheral Vascular Disease, *Arch. Surg.* 40:286 (Feb.) 1940.

11. Holman, E.: (a) Surgery of Large Arteries. *Ann. Surg.* 85:173, 1927. Holman, E., and Edwards, M. E.: (b) New Principle in Surgery of the Large Vessels, *J. A. M. A.* 88:909, (March 19) 1927. Linton, R. R.; Morrison, P. J.; Ulfelder, H., and Libby, A. L.: Therapeutic Venous Occlusion, *Am. Heart J.* 21:721, 1941. Pearse, H. E.: A New Explanation of the Improved Results Following Ligation of Bypass Artery and Vein, *Ann. Surg.* 86:850, 1927.

12. Linton, R. R.: Treatment of Acute Arterial Occlusion by Means of Intermittent Venous Occlusion, *Arch. Surg.* 46:395 (March) 1943. Pemberton, J. and McCaughan, J. M.: Traumatic Lesions of Arteries: Indications for the Therapeutic Ligation of Veins, *Am. Surg.* 96:1103, 1932. Makins.²

8. Burns, Shock, Wound Healing and Vascular Injuries, Military Surgical Manuals, National Research Council, Philadelphia, W. B. Saunders Company, 1943. vol. 5.

9. Halsted, W. S.: The Effect of Ligation of the Common Iliac Artery on the Circulation and Function of the Lower Extremity, *Bull. Johns Hopkins Hosp.* 3:191, 1912.

duced. It is felt that the patient's life was probably saved by this step, since a minor pulmonary infarction did develop following the operation.

The second stage was the operation to eradicate the arteriovenous fistula. According to the literature,¹³ the method of choice is excision of the fistula and the vessels involved after ligation and division of the artery and vein proximal and distal to it. It was impossible to carry out this procedure in this case, because the tremendous enlargement of the inferior vena cava and the right common iliac vein made it impossible to free either for the purpose of ligation. In addition, it was considered unnecessary because of the type of operation that was performed and also since the preliminary sympathectomy of the lumbar ganglions had been carried out to safeguard the circulation of the extremity.

Direct adequate exposure in the surgical treatment of large blood vessels is the sine qua non of success. For this reason a transperitoneal approach was utilized. The abdomen was opened through a right paramedian incision. The intestines had been deflated by a Miller-Abbott tube, so that they were readily displaced upward to expose the region of the bifurcation of the aorta and of the inferior vena cava. The fistula was localized by digital pressure over the right common iliac artery. The opening could be palpated readily through the anterior wall of the artery and occluded by pressure with the tip of the index finger. The posterior portion of the peritoneum was incised to expose the lower end of the aorta, the entire length of the right common iliac artery and the proximal end of the left common iliac artery. The right ureter was displaced lateralward. Before an attempt to dissect out the vessels at the site of the fistula was made, control of the arterial inflow both proximal and distal to it was obtained. First, a tourniquet clamp (fig. 1) was applied to the aorta just proximal to its bifurcation. Then similar clamps were placed on the proximal end of the left common iliac artery and on the right common iliac artery distal to the fistula to prevent reflux of blood from the collateral circulation. By closing all three clamps it was then possible to shut off completely the arterial blood flow through the fistula.

Dissection of the right common iliac artery was therefore possible with relative safety and peace of mind, despite an unusual amount of scar tissue about the great vessels in this region. Explora-

tion of the proximal end of the right common iliac artery revealed that the fistulous opening lay about 1.5 cm. from the aortic bifurcation. It was possible to separate this portion of the common iliac artery from the underlying inferior vena cava, so that a fourth tourniquet clamp could be applied at this point; thus the portion of the right common iliac artery containing the fistula was isolated between two clamps.

The fistula was eradicated from the circulation by ligation and division of the right common iliac artery proximal and distal to it. The iso-

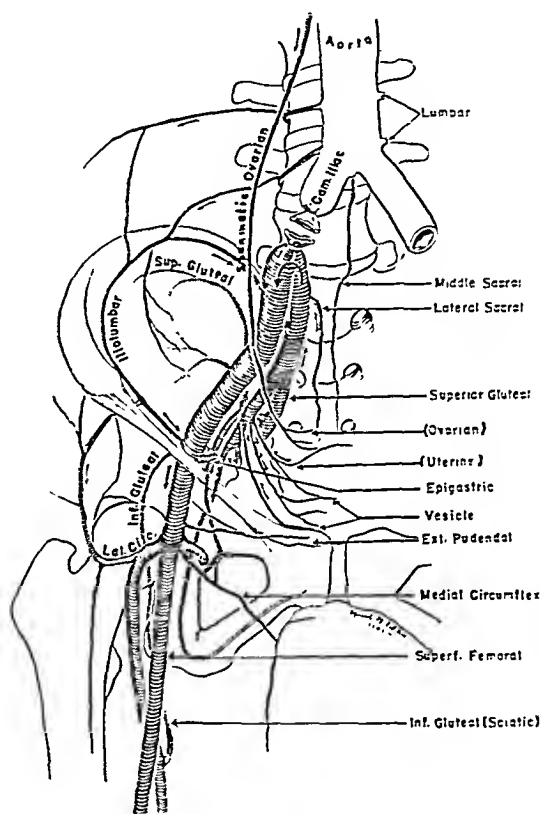


Fig. 5.—A diagrammatic drawing to show the sources of the collateral arterial blood supply to the lower extremity following interruption of the common iliac artery. These consisted of two groups of arteries: (1) the hypogastric artery and its tributaries of the ipsilateral and the contralateral side of the body, namely, the iliolumbar, lateral sacral, superior and inferior gluteal, internal pudendal and superior and inferior vesicle arteries and (2) the inferior epigastric, superficial epigastric, deep circumflex iliac and superficial circumflex iliac arteries.

lated portion of the right common iliac artery, which contained the fistula, was about 2 cm. in length. It was left in situ attached to the inferior vena cava, resection of it being unnecessary because there were no collateral branches entering it, which if present might cause a recurrence (fig. 2).

13. Elkin, D. C.: Vascular Injuries of War. *Ann. Surg.* 120:284, 1944. Holman.² Makins.³ Reid and McGuire.¹

Preservation of the collateral circulation after division of a major artery to an extremity is of vital importance in the prevention of gangrene. Since there are no tributaries of any significance arising from the right common iliac artery between its origin and termination, interruption of it will not interfere with the collateral circulation to the lower extremity providing its bifurcation into the external iliac and the hypogastric artery is preserved. In this case extreme care was taken not to damage this major bifurcation, since preservation of it permits arterial blood, which enters the hypogastric artery through its numerous tributaries by anastomoses from the same and the contralateral side of the body, to pass directly into the external iliac artery and then peripherally through the main arterial system of the extremity. If both the external iliac

reveals that the main arteries through which blood can enter may be divided into two groups (1) the hypogastric artery and its tributaries and (2) the tributaries of the external iliac artery, namely, the inferior epigastric, superficial epigastric, deep circumflex iliac and superficial circumflex iliac arteries. The tributaries of the hypogastric artery, which contribute to the collateral blood supply, are the iliolumbar, lateral sacral, superior and inferior gluteal, internal pudendal and superior and inferior vesicle arteries. Blood will enter these not only through anastomoses on the same side of the trunk but through anastomoses with the arteries on the opposite side of the body.

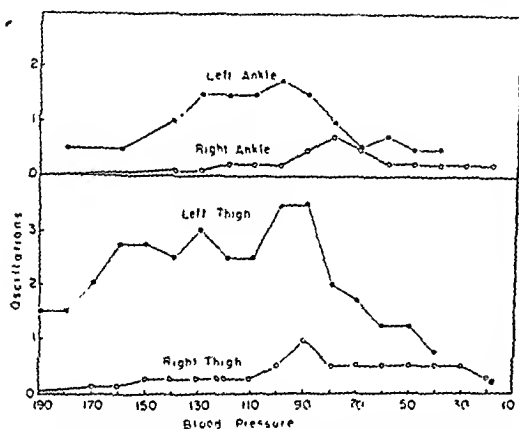


Fig. 6.—Graphs to show the oscillometric readings on the patient's legs two weeks after eradication of the fistula, which confirm the clinical observation that pulsations were detectable in the right posterior tibial and the dorsalis pedis arteries. The oscillations in the right leg were of much less caliber than those in the left, with its normal arterial system, but the fact that they were present and measurable, even with the main artery to the extremity interrupted, should not be overlooked.



Fig. 7.—A photograph showing the patient's legs two weeks after interruption of the right common iliac artery. The right leg appears normal except for slight muscular atrophy. The bandage covers the scar of the abdominal incision, made to expose the great vessels and the fistula.

and the hypogastric artery are interrupted reflux of arterial blood from the latter, which is the major portion of the collateral arterial supply, is prevented. This predicates a reversal of the flow of blood through the hypogastric artery. An analysis of the hemodynamics under these conditions supports this theory. After ligation of the common iliac artery the arterial blood pressure falls considerably distal to the point of interruption. Owing to the lowered pressure, blood enters the arterial tree through any and all channels connected with it, in which the pressure is at a higher level. Examination of the anatomic structure of these collateral channels (fig. 5)

Since interruption of the major artery to an extremity causes a pronounced fall in the blood pressure and a decrease in the flow of blood distal to the point of ligation, spontaneous thrombosis is likely to occur. For this reason, in order to safeguard the collateral circulation of the extremity, heparin was administered intravenously for forty-eight hours following the second stage of the operation.

nistration was stopped at the end of this time, after it was ascertained that the arterial circulation to the foot was adequate. The coagulation time of the blood was maintained approximately thirty minutes.

Palpable pulsations were observed in the right dorsalis pedis and the posterior tibial artery for the first time four days following eradication of the fistula. This in itself indicated the adequacy of the collateral circulation. This observation was confirmed by the oscillogram (fig. 6). The presence of pulsations in these peripheral arteries, despite interruption of the main arterial supply to the extremity, is best explained by the fact that arterial blood was entering the main arterial system of the extremity through all arterial tributaries distal to the point of ligation. The total amount of arterial blood thus entering the external iliac and the femoral artery was sufficient in volume to produce pulsations distal to the point of arterial interruption.

The ability of our patient to walk several miles without intermittent claudication fifteen months after interruption of the common iliac artery is additional evidence of the adequacy of the collateral arterial circulation. Halsted,⁹ in an analysis of the cases which he studied, noted that in several of them, including 1 of his, the patients were incapacitated because of cramp-like pain in the limb on walking short distances, which he attributed to ischemia. The adequacy of the circulation in the limb in the case reported here was in part due to ablation of the first, second and third lumbar ganglions, which abol-

ished vasoconstrictor impulses and maintained a constant state of maximum vasodilatation.

CONCLUSIONS

Injury to the inferior vena cava and the right common iliac artery may occur during the radical removal of a ruptured intervertebral disk between the fourth and fifth lumbar vertebrae. An arteriovenous fistula between these two vessels may be produced by an instrument which is forced through the anterior longitudinal ligament, transfixing the inferior vena cava and the posterior wall of the right common iliac artery. Serious hemorrhage at the time of the accident may not occur, so that the arteriovenous communication may exist for some time before it is recognized. The first symptoms of its presence may be those of cardiac decompensation.

Ligation and division of the common iliac artery proximal and distal to the fistula were sufficient to cure the condition and reestablish the cardiovascular system to normalcy.

Interruption of the common iliac artery is apparently compatible with adequate circulation and practically normal function of the lower extremity if a preliminary sympathectomy, in which the first, second and third lumbar ganglions are removed, has been carried out.

Therapeutic venous occlusion by simultaneous interruption of the external iliac vein was probably an added factor in establishing the collateral circulation immediately after interruption of the common iliac artery.

TRAUMATIC HEMOTHORAX

DECORTICATION IN THE TREATMENT OF THE CHRONIC UNINFECTED TYPE

MAJOR FRANK P. COLEMAN

MEDICAL CORPS, ARMY OF THE UNITED STATES

The respiratory disability associated with the later stages of wounds of the thorax incurred during war is a real problem. Infection is primarily responsible for the disability in the majority of cases; however, organization of blood within the pleural cavity unattended by sepsis is not uncommon and often leads to an even greater degree of respiratory invalidism. Favorable experiences in the surgical management of the latter condition by decortication of the lung has prompted this communication.

The trend of treatment of acute traumatic hemothorax in this war has been conservative.¹ In the forward zones of combat modern methods of preventing and relieving shock are efficiently executed, thus saving many lives. Respiratory distress is readily recognized and relieved by aspiration of blood without replacement with air. In the forward higher echelons the pleural cavity is emptied of the bloody effusion as soon as possible by repeated aspiration without replacement with air.² There is some evidence to support the thesis that the sooner the blood is removed from the pleural cavity the less is the chance of septic complications.³ On the other hand, the sequence of events precipitated by the presence of blood within the pleural cavity does not warrant the conclusion that early aspiration will prevent the deposition of fibrin. It is the organization of deposits of fibrin which leads to the later varying degrees of respiratory disability in an otherwise uncomplicated acute traumatic hemothorax.

MECHANISM OF THE DISABILITY

When blood escapes into the pleural cavity it apparently undergoes early formation of a clot.

1. Kirk, N. T.: *Surgical Care of the Wounded in the U. S. Army, Surgery* 15:211 (Feb.) 1944.

2. (a) Edwards, A. T.: *Traumatic Hemothorax, Lancet* 1:97 (Jan. 23) 1943. (b) Linberg, B. E.; Matsyev, I. E., and Acutin, M. N., cited, *Traumatic Hemothorax*, editorial, *ibid.* 1:315 (March 4) 1944. (c) Nicholson, W. F., and Scadding, J. G.: *Penetrating Wounds of the Chest: A Review of 291 Cases in the Middle East, ibid.* 1:300 (March 4) 1944.

3. Edwards, 2a. Nicholson and Scadding.^{2c}

The views expressed by Elliott⁴ offer an explanation for what appears to be the absence of clotting of blood within the pleural cavity. The author stated "that the effused blood very rapidly passes through the clotting process, but that coagulation is interfered with by the respiratory movements so that the fibrin is to a considerable extent whipped out of the blood." If blood enters the pleural cavity is slow, the blood is rapidly deprived of fibrin by the movements of the diaphragm and the heart. The pleura is irritated by the blood, and an effusion is poured out. The blood free of fibrin mixes with the effusion resulting in a fluid hemothorax, which does not undergo formation of a clot on removal from the pleural cavity. The fibrin is usually deposited in a dependent location. If bleeding into the pleural cavity is rapid, sufficient agitation may not be present to bring about defibrination of the blood, and a solid hemothorax results. Other factors which favor formation of a massive clot within the thorax are extensive destruction of tissue and retention of foreign bodies within the pleural cavity.

The pleura is able to cope with the deposit of fibrin in a small hemothorax. The associated effusion is either aspirated or absorbed. In such cases no functional incapacity results. On the other hand, deposition of fibrin accompanied by a process of organization may be sufficient to lead to the formation of dense pleural adhesions. The mobility of the diaphragm, thoracic wall and lung is restricted. In such cases a routine roentgen film may reveal only slight haziness over the base of the lung; however, the limitation of the motion of the diaphragm is readily obvious during fluoroscopy, and a deposit of fibrin is identified in the costovertebral sulcus by lateral roentgenograms of the chest. The mechanism of the disability associated with organization of a large hematoma within the cavity is obvious. The thick wall of the hematoma fixes the pleural surface of the ribs, interfering with the normal widening of intercostal spaces during inspiration. Org

4. Elliott, T. R.: *Gunshot Wounds of the Thorax, Brit. M. J.* 1:442 (April 12) 1919.

rous tissue contracts, drawing the ribs closer together, and the normal longitudinal curves of the ribs are lost. The involved hemothorax becomes flattened and immobile. The diaphragm when involved loses its function entirely. The involved portion of the lung is usually normal, but it cannot perform its function when it is encased in a fibrous encasement.

THE DISABILITY

The temporary disability associated with uncomplicated hemothorax has been attributed to the organization of fibrin within the pleural cavity. Pain and shortness of breath are the primary symptomatic manifestations. I have observed repeatedly persistence of pain in the chest following what appeared to be otherwise successful treatment of acute hemothorax. Dyspnea was not a prominent symptom. Detailed roentgenograms and fluoroscopic examination of the chest as a rule revealed some fixation of the diaphragm and a deposit of fibrin in the costo-vertebral gutter. Recent reports have revealed that patients with acute uncomplicated hemothorax do not return to military duty for three months and that the majority complain of pain in the chest for an additional three months.^{2c} The symptomatic manifestations and the disability associated with obvious chronic organized hemothorax do not require a great deal of comment. Patients with this complication are unfit for military duty. They are chronically ill. A low grade fever is usually present, and even in the absence of infection the temperature may reach a daily level as high as 102 F. There is distinct pallor to the skin, and frequently secondary anemia is present. Dyspnea on exertion and pain in the involved side of the chest are common symptoms. The hemothorax is flattened and immobile. There is compensatory emphysema of the uninvolved lung. The compensatory activity of the contralateral lung exaggerates the deformity produced by the chronic organized hemothorax.

INCIDENCE OF CHRONIC UNINFECTED HEMOTHORAX

It is difficult to come to any conclusion relative to the frequency of formation of a massive blood clot within the pleural cavity. Only sporadic cases appear in the literature. Infected hematomas have been treated as empyema and classified in the literature under septic hemothorax. Meakins and Walker³ were the first to point out

the close connection between the development of deformity of the chest and the time that the pleural cavity was allowed to retain the fluid, irrespective of whether the fluid was sterile or infected. These authors cited 3 cases in which soldiers were given a medical discharge from the army on account of invalidism which was produced by the organization of blood within the pleural cavity. During World War I Elliott⁶ reported an incidence of 3 cases of formation of a massive uninfected clot in a series of 156 cases of hemothorax. Nicholson and Scaddings^{2c} recent report revealed formation of a massive clot in 6 of 125 cases of uninfected and in 6 of 62 cases of infected hemothorax.

MANAGEMENT

During the treatment of the later stages of thoracic wounds in the first World War it soon became obvious that an organized uninfected hemothorax produced many of the severe and crippling deformities. Difficulty in managing this condition is best illustrated by Elliott's⁶ statement: "It is paradoxically true that recovery of the chest from the crippling results of a large haemothorax may be more rapid if sepsis occurs than if the collection remains sterile." Turner⁷ and Moynihan⁸ recognized that removal of the foreign body from the thorax without freeing the lung and thoracic wall of adhesions was a useless procedure. These surgeons described the disability produced by an organized hemothorax and in a limited number of cases applied the principles and technic of decortication of the lung, which was first described by Fowler⁹ in 1893. Since 1920 little attention has been given to the chronic type of hemothorax with the exception of Smithy's¹⁰ revival of interest in the management of this condition.

In the treatment of chronic traumatic uninfected hemothorax, the surgical approach is governed somewhat by the site of the formation of the clot. The blood clot usually assumes a dependent position within the pleural cavity, ly-

6. Elliott, T. R.: Some Statistical Results of the Treatment of Chest Wounds, *Lancet* 2:371 (Sept. 8) 1917.

7. Turner, G. G.: The Later Stages of Gunshot Wounds of the Chest, *Surg., Gynec. & Obst.* 28:17 (Jan.) 1919.

8. Moynihan, B.: The Surgery of the Chest in Relation to Retained Projectiles, *Brit. J. Surg.* 7:444 (April) 1920.

9. Fowler, G. R.: A Case of Thoracoplasty for Removal of a Large Cicatricial Fibrous Growth from the Interior of the Chest, the Result of an Old Empyema, *M. Rec.* 44:838 (Dec. 30) 1893.

10. Smithy, J. G.: Traumatic Hemothorax with Special Reference to Chronic Persistent Types, *J. Thoracic Surg.* 12:338 (April) 1943.

5. Meakins, J., and Walker, T. W.: After-Effects of Wounds of the Chest, and Their Treatment, *Canad. J. A. J.* 8:910 (Oct.) 1918.

ing in the costovertebral gutter and overlying the diaphragm. Access to this region is readily accomplished by making a posterolateral incision, and the pleural cavity is entered through the seventh or eighth intercostal space. The wall of the hematoma is encountered on division of the intercostal muscles and the parietal pleura. A cleavage plane between the wall of the hematoma and the pleura may be developed with ease, owing to the fact that these structures are bound together by only a light network of vascular and fibrous tissue. The wall of the hematoma is freed from the adjacent structures by blunt dissection, working away from the thoracic wall and lung. The index finger or a blunt gauze dissector has proved satisfactory for this procedure (fig. 4). It is possible to mobilize a large hematoma in this manner without disruption of its physical characteristics (fig. 2). After the lung, the diaphragm and the thoracic wall have been freed of the hematoma, the underlying pleura may be observed to be practically normal. It is not thickened, and it still has a somewhat smooth and glistening appearance. The previously constricted diaphragm and lung will function in a normal manner with removal of the fibrous encasement. In a clotted hemothorax of less than three weeks' duration the cleavage plane between the pleura and the wall of the hematoma is not sharply demarcated. At this stage the wall of the hematoma has not become well organized and there is persistence of the edema of the adjacent pleura. Early removal of the deposit of fibrin does not permit the ready reexpansion of the lung, which is so admirably demonstrated when this structure is freed of a well organized hematoma.

The following case reports emphasize the clinical manifestations and the morbid anatomic structure of a chronic organized uninfected hemothorax. The successful application in each instance of Fowler's principles and technic of decortication of the thoracic wall, diaphragm, mediastinum and lung is described.

REPORT OF CASES

CASE 1.—A white soldier aged 19 sustained a bullet wound of the left side of the thorax on Sept. 12, 1943. The bullet entered the anterior triangle of the neck and in its course traversed the pleura, the lung and the second, third and fourth dorsal vertebrae. There was no wound of exit. He was treated for shock, and three weeks later the bullet was removed from the body of the fifth dorsal vertebra. No attempt was made to aspirate the left side of the chest until three weeks following the injury. At this time it was impossible to remove the collection of blood in the left pleural cavity. Since the date of injury, he had suffered from severe dyspnea, extreme pallor, daily low grade fever

and progressive development of a deformity of the left side of the chest.

He was transferred to my service for definitive treatment. Physical examination disclosed a thin, pale, undernourished and chronically ill man. The left side of the chest was fixed, sunken and flat. Overactive respiratory excursions on the right side stood out in strong contrast to the immobility on the left. The left side of the chest had the appearance of an old empyema. The percussion note over the entire left hemithorax was flat and accompanied by an absence of breath sounds; however, in the left infraclavicular region the percussion note was hyperresonant and the breath sounds were exaggerated. On the right, physical signs of a compensatory emphysema were present. The routine laboratory tests gave negative results. A roentgenogram of the chest revealed a dense opacity involving the entire left side of the thorax with an emphysema on the right (fig. 1). Fluoroscopic examination revealed fixation of the diaphragm on the left.



Fig. 1 (case 1).—Roentgenographic view of the thorax sixty-seven days after a gunshot wound, showing chronic organized hemothorax.

Numerous attempts to aspirate the left side of the chest were unsuccessful, and only a few cubic centimeters of a brownish fluid was obtained. This fluid failed to grow organisms on culture.

On Nov. 18, 1943, the pleural cavity was entered through a posterolateral incision. By means of an incision through the seventh intercostal space the wall of the hematoma was encountered and found to be moderately adherent to the parietal pleura. By digital manipulation the hematoma was easily separated from the parietal and visceral pleuras. It contained approximately 500 cc. of old blood, and its wall was 2 cm. thickness. Anteriorly the hematoma terminated at the lateral border of the sternum, while posteriorly it was anchored to the aorta. It extended from the dome of the thorax to the diaphragm (fig. 2). The left lung was about the size of a grapefruit; however, neither the visceral nor the parietal pleura was thickened, and the lung readily reexpanded on completion of decortication.

1. The left pleural cavity was drained by an inter-tal tube, and the wound was closed in layers. The drainage tube was connected to an under-water seal, and 16 cm. of negative water suction was applied to attain reexpansion of the lung.



Fig. 2 (case 1).—Gross appearance of a chronic organized hematoma.



Fig. 3 (case 1).—Roentgenogram taken three weeks postoperatively. Reexpansion of the left lung is now complete.

The postoperative course was entirely uneventful. The drainage tube was removed on the first postoperative day, at which time there was complete reexpansion of the left lung. Three weeks postoperatively, there was almost a 100 per cent return of function in the

left lung and the soldier was no longer dyspneic on physical exertion (fig. 3).

CASE 2.—A white officer aged 32 sustained a bullet wound of the right side of the chest on Dec. 27, 1943. A bullet from a machine gun entered the right side of the chest 2 inches (5 cm.) lateral to the right border of the sternum in the fourth intercostal space. There was no wound of exit. He was given immediate treatment for shock, and no attempt was made to aspirate a hemothorax on the right side. During the ensuing five weeks he continued to have a low grade fever, lost weight, complained of a sense of constriction in the right lower portion of the chest and was dyspneic on exertion.

Physical examination at the time of his transfer for definitive treatment disclosed a moderately anemic and asthenic person. There was a scar marking the wound of entrance in the fourth intercostal space 2 inches

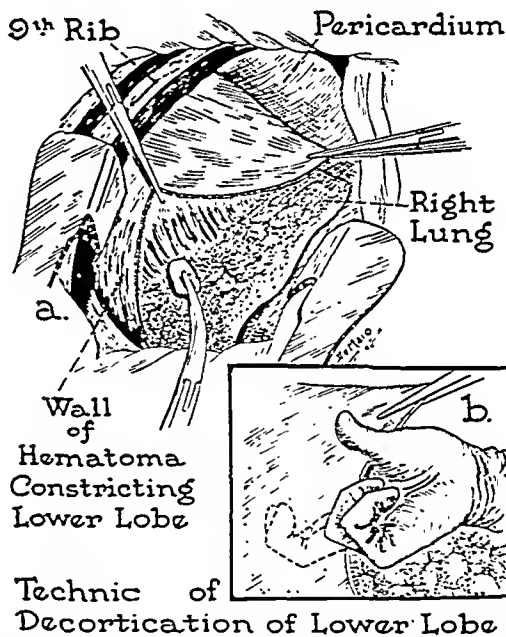


Fig. 4.—Illustrations of the operative procedure in case 2.

lateral to the right border of the sternum. He was chronically ill and dyspneic on exertion. There was a definite decrease in the respiratory excursions of the right side of the chest. The lower portion of the thoracic wall was rigid and flattened. The intercostal spaces were narrow, and the entire right side of the chest was contracted as well as limited in motion. Dulness accompanied by decreased breath sounds extended well above the angle of the scapula and high in the axilla on the right. Tactile fremitus was decreased in this region. There was compensatory emphysema on the left. The routine laboratory tests gave negative results. Roentgenologic examination revealed four foreign bodies, ranging in size from 3 by 4 mm. to 9 by 15 mm., embedded in the right side of the chest. There was diffuse haziness over the entire right lower portion of the chest, and the lower and middle lobes of the right lung were displaced toward the midline. Aspiration on numerous occasions proved unsuccessful, yielding only 5 to 10 cc. of a brownish fluid. This fluid failed to grow organisms on culture.

On Feb. 5, 1944, a right posterolateral incision was made, the right pleural cavity being entered through the eighth intercostal space. A well organized hematoma, containing approximately 700 cc. of old blood, compressed the lower and middle lobes of the lung. Removal of the contents of the hematoma did not permit reexpansion of the lung and resumption of excursions by the diaphragm. These structures were constricted and rendered immobile by the thick wall of the hematoma. The constricting walls of the organized hemothorax were removed by sharp and blunt dissection. This process of decortication permitted total and complete reexpansion of the two lobes of the lung, and the diaphragm resumed its normal function. The foreign metallic bodies, which lay in a superficial position within the lower lobe, were removed. An intercostal tube was inserted into the right pleural cavity and connected with an under-water seal. The wound was closed in layers.

The postoperative course was entirely uneventful. Clinical and roentgen examination revealed complete reexpansion of the lung on the first postoperative day. Two weeks postoperatively the patient was entirely asymptomatic and gratified with the ease of respiration. He has returned to duty.

CASE 3.—A white soldier, 32 years of age, with eighteen months of service in the army, had been entirely asymptomatic until the early part of November 1943. At this time he noticed constant and ill defined pain in the lower part of the right side of the thorax. A roentgen examination revealed a tumor mass in the posterior mediastinum extending from the level of the seventh dorsal vertebra to the level of the tenth dorsal vertebra. The tumor mass was irregular in outline but sharply demarcated. The preoperative diagnosis was ganglioneuroma of the posterior mediastinum, which was confirmed on removal of the tumor.

On November 16 a thoracotomy was performed, the right pleural cavity being entered through the seventh intercostal space. A tumor mass, measuring 10 by 6 by 5 cm., incorporated the sympathetic trunk, the greater and lesser splanchnic nerves and the seventh, eighth and ninth intercostal nerves. The overlying pleura was removed with the tumor mass. This left a considerable area in the costovertebral gutter denuded of its normal covering. The wound was closed in layers, and the pleural cavity was not drained.

His postoperative course was entirely uneventful with the exception of accumulation of blood in the right pleural cavity, which could not be evacuated with a no. 16 aspirating needle. Thoracentesis was carried out on the first postoperative day and yielded only a small quantity of dark blood. Thereafter, repeated aspirations failed to yield more than 10 cc. of blood. A roentgen film of the chest revealed an accumulation of blood in the right side of the thorax lying primarily in the costovertebral gutter at the site of resection of the

tumor mass. During the ensuing sixteen cultures of a small amount of fluid obtained by aspiration yielded no growth. The wound, by primary intention; however, the patient has a low grade fever.

On December 2 the right pleural cavity through the primary thoracotomy wound, which contained 500 cc. of old blood, lay vertebral gutter and compressed the upper right lung. The walls of the hematoma were defined. The visceral and the parietal edematous and studded with shaggy collections undergoing early organization. The upper lobe did not readily reexpand after the fibrin was removed; however, there was definite improvement. A no. 32 rectal tube was introduced through the intercostal space and led well up to the thoracic cavity on the right side. The tube was connected to an under-water seal. The chest was closed in layers. Reexpansion of the right lung was complete on the first postoperative day, an intercostal tube drain was removed. Convalescence was uneventful. In three days the temperature was normal and there was no further accumulation of blood in the right side of the thoracic cavity. Two weeks postoperatively a roentgenogram of the chest revealed complete reexpansion of the right pleural cavity to be free of pleural exudate. The soldier was returned to duty.

SUMMARY

The apparent successful treatment of traumatic hemothorax does not always prevent varying degrees of later respiratory impairment. Temporary persistence of pain in the chest associated with mild degrees of dyspnea is an uncommon sequela. These symptoms may be ascribed to the organization of fibrin in the pleural cavity.

The organization of a large uninfected hemothorax leads to serious respiratory and deformity of the chest. This coupled with futile attempts at resection demands the institution of some measure to prevent patients with this complication from the semi-invalidism or invalidism. Application of the principles and technique of decortication involving anatomic structures seems to be a requirement.

Cases of chronic organized hemothorax are cited which illustrate the successful surgical management by decortication of the lung, the chest wall and diaphragm.

SLIPPING OF THE UPPER FEMORAL EPIPHYSIS

DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS

WILLIAM T. GREEN, M.D.

BOSTON

If slipping of the upper femoral epiphysis or epiphysiolysis is recognized at an early stage and proper treatment is instituted, the prognosis should be excellent. If it is not recognized until considerable displacement has occurred, it may produce severe crippling, whatever treatment is followed. It is the purpose of this paper to stimulate early recognition of the condition and to report experiences with various methods of treatment.

This report includes 26 patients with slipping of the upper femoral epiphysis in 36 hips.¹ They represent the total number of patients admitted to the Children's Hospital, Boston, in the last thirteen years with certain additions.^{2a}

The result in 28 of the 36 hips has been evaluated after an average interval of six and three-tenths years. Of the remainder, 6 have been treated too recently for evaluation and 2 were not treated. All but 5 were examined in 1944, and the present status of all but 2 hips in the series is known. Roentgen study accompanied clinical examination in all instances.

MECHANISM AND RELATED FACTORS

The process depends on a weakening of the connection between the head and neck of the femur at the metaphysis, with subsequent displacement of the head on the neck. The neck of the femur on weight bearing tends to ride upward and anteriorly, with increasing external rotation. The head in turn tends to migrate posterior and inferior to its usual position (fig.

9 *A* and *B*). Displacement may be of any degree, from an undetectable amount to complete displacement. Owing to the natural direction of the neck of the femur, external rotation is the essential factor in the displacement.

If the slipping is of any degree the blood vessels on the anterior and the lateral surface of the neck are interrupted. The circulation to the head of the femur must then come by way of the ligamentum teres, a route which is variable and undependable, and by way of the vessels on the inferior-posterior aspect of the neck, particularly by way of those in the retinacula of Weitbrecht (fig. 9 *A* and *B*). With displacement of the head posteriorly and downward the latter vessels are shortened, as is the periosteum. Since the slipping is usually a gradual and repeated process, this shortening becomes fixed, with secondary fibrosis and formation of osteoid, which becomes calcified. Therapeutic measures designed to correct the deformity may interrupt this essential circulation, producing aseptic necrosis of the head, not only by tearing or cutting the retinacular vessels but by strangulating them through tension.

Although the cause of slipped epiphysis is unknown, certain related facts should be emphasized. It occurs at a particular period in development, most frequently between the ages of 10 and 15 years, and in the collected cases the average age of boys is 2 years older than that of girls. This reflects approximately the increased degree of skeletal maturation of the female. The process occurs at a time of rapid growth. The children affected are usually obese or large. Nineteen of the children in this series were extremely obese to obese, 6 were large but not fat and 1 was of average build. The condition is frequently bilateral, and in 10 of my patients both hips were affected. Two of the 26 patients had a sibling with the same condition.

Trauma is often described as an etiologic factor. In this series there was a history of trauma of significant degree preceding the first symptom for 5 patients. For 21 there was no known antecedent trauma, although for several

From the Department of Orthopedic Surgery, the Children's Hospital and the Harvard Medical School.

Read in the Section on Orthopedic Surgery at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 15, 1944.

1. Sex: 15 boys; 11 girls. Bilateral involvement: 10 (7 males); 6 had bilateral lesions on their first admission to the hospital. Unilateral involvement: 16. Average interval between initial symptoms on the two sides: fourteen months. Longest interval between initial symptoms on the two sides: thirty-three months. Side: right 17; left 19. Girls' average age: $10\frac{1}{2}$ years; youngest 7 years; oldest $12\frac{1}{2}$ years. Boys' average age: 11 years; youngest $7\frac{1}{2}$ years; oldest $13\frac{1}{2}$ years. Average duration of symptoms on admission: 5 months.

1a. Patients treated at the Peter Bent Brigham Hospital by me are included.

of the latter trauma did precipitate the acute symptoms.

Certain comments may be made regarding these factors. It would appear that trauma has the role of provoking displacement in an antecedent condition. This is suggested by the frequency with which the condition is bilateral as well as by the history. The high frequency of bilateral disease would indicate a fundamental predisposition in the person affected, and in this the familial incidence is probably significant. The fact that many of the patients are of the so-called fat "endocrine type" may mean that there is an unknown endocrine factor, or it may merely represent the increased stress which the added weight induces. A shearing stress peculiar to the metaphysis of the femur exists, and this is increased by genu valgum, which is common in these patients.

The integrity of the connection of any epiphysis to the shaft depends largely on the binding effect of the periosteum. It is possible that with the rapid growth and the changes in the character of the periosteum which occur at this age, the periosteum loses its firm binding character² and allows the displacement. Howorth³ emphasized that synovitis exists before the slipping occurs, but whether this is primary or secondary is unknown. An abnormality in the evolution of the vascular supply to the area at this particular age may be responsible, but this again has not been proved.

It is suggested, however, that there is more to the process than simply displacement of the head on the neck. In 1 of the patients in this series, for example, there was complete degeneration of the opposite joint without any recognizable slipping of the epiphysis or other discernible cause.

CLINICAL PICTURE

A child of the age peculiar to this disease, usually obese or large, acquires an antalgic hip limp, which may be intermittent or constant. All but 1 of my patients had a primary complaint of limp. Pain, though not mentioned by 5 of the patients, is usual. Activity increases the symptoms. The pain may be in the hip or groin, the anterior or anterolateral portion of the thigh or the knee. It may be present in any one of these areas or in any combination of them.

Two patients in this series who complained solely of pain in the knee had their knees exam-

ined, including the taking of roentgen with no attention paid to their hips. These patients was sent home and two later while walking across the floor had complete displacement of the epiphysis. It was unusual for the patients in this series to have had previous medical observation over a relatively long period without the condition recognized.

Even when the symptoms are mild, physical examination will usually disclose limited internal rotation, flexion and abduction involved hip with pain and muscular spasm at the extremes of these motions. Hyperextension of the hip may be increased. Limited internal rotation is usually the earliest suggestive physical finding. Often the hip tends to go into external rotation as it is flexed.

As the process increases the limp and pain increase. The gait may be frankly waddling if the involvement is bilateral. Spasm may be present on all motions. A fixed external rotation deformity may develop. It was present in 50 per cent of the patients in this series.

If acute displacement occurs, the signs are those of a fractured neck of the femur: extreme muscular spasm, the extremity held in external rotation.

Frequently there is a history of minor trauma or discomfort for some weeks or months, followed by relatively mild trauma, which precipitates the acute symptoms.

ROENTGEN EXAMINATION

Careful roentgen examination of the hips, including the taking of lateral projections, is essential. The lateral films are best taken in the hip position, that is with the hip externally rotated. The earliest findings are rarefaction of the neck adjacent to the epiphysal line and minimal displacement of the neck anteriorly on the head (fig. 3 A and B). The latter can be seen only in the lateral projection. The films must be of excellent quality before a report of negative results is given, if the history and physical signs are suggestive; in fact, in such cases the patient should be carefully observed and the roentgen examination repeated after a short interval.

If there is much displacement the condition is recognized easily in both the anterior and the lateral projection. If the slipping is of some duration, irregular callus may be seen filling the angles between the head and the neck. At this stage the picture in the neck may be one of mottled density and rarefaction.

If slipped epiphysis exists it should be considered an emergency, since at any time marked

2. Key, J. A.: Epiphyseal Coxa Vara. *J. Bone & Joint Surg.* 8:53-117, 1926.

3. Howorth, M. B.: Slipping of the Upper Femoral Epiphysis. *Surg., Gynec. & Obst.* 73:723-732, 1941.

crease in the displacement may occur. If it is the prognosis is greatly impaired.

TREATMENT AND RESULTS

In considering the results of treatment for slipped epiphysis it should be emphasized that individual cases are not directly comparable, whether owing to variations in the degree of displacement, duration of the disturbance or other factors. What might be a good result in 1 patient, based on the original condition, might be a poor result in another.

The results in this paper are evaluated not on the basis of improvement from the original condition but on the basis of normal painless motion. Using the normal hip as a standard as not satisfactory, since in many of the

Closed Manipulation with the Patient Under Anesthesia with Spica Fixation.—Three patients in this series were treated by this method, and the results have been evaluated after an average of ten and three-tenths years (table 1).

My interest in slipping of the upper femoral epiphysis originated from contact with a patient who had closed reduction of a severely displaced upper femoral epiphysis. Her history follows.

J. M., a girl of 11 years, was seen at the Children's Hospital on June 27, 1931, with the complaint of severe pain in the left hip following a fall one hour before. She had had mild pain in this hip and limp for six weeks preceding the fall, which were said to have followed bending exercises in school. They had recurred with exercises and were relieved by rest. The family and the past history were irrelevant except for the fact that the family was generally obese and that the child herself had been treated for knock knees.

TABLE 1.—Results of Miscellaneous Treatment

Patient	Years Followed	Estimated Original Displacement, Cm.	Treatment	Index of Motion (Ferguson-Howorth)	Pain	Significant Deformity Change	Arthritic Change	Shortening	Limp	Result	
A. C.	12½	1.5	Thomas brace with patten	57.8	0	—	0	Bilateral	0	Good — Other side slipped while brace was being worn	
	12	1.5	Thomas brace with patten	57.2	0	—	0	Bilateral	0	Good —	
M. H.	6	0.5	Traction, 4½ mo.; Thomas brace with patten and crutches, 4½ mo.	106.3	0	0	0	2 cm.	0	Excellent	
B. S.	3	1.3	Traction, 5 mo.; crutches	70.3	0	++	?	Bilateral	0	Good —	
		1.5	Traction, 5 mo.; crutches	56.2	Occasional	Severe	Cup	Bilateral	—	Poor. Seen first 7 and 14 months after onset; severe degenerative changes on admission	
J. M.	11	Severe	Manipulation and spica	32	0	+++	+++	4 cm.	+	Poor; aseptic necrosis; other h.p. stiff without slipping	
E. L.	10	Severe	Manipulation and spica	61.5	0	++	?	0	Bilateral	0	Fair
	9	?	Manipulation and spica	49.5	0	++	+	0	Bilateral	—	Poor —

patients the process was bilateral. In order to express the amount of motion in the hips by a single composite figure the coefficient proposed by Ferguson and Howorth,⁴ in which 90 to 110 is estimated as normal, has been used.

The various methods of treatment used in this series may be classified as follows: (1) closed reduction with spica fixation; (2) traction-spica-traction method without manipulation; (3) skeletal fixation in situ (without arthrotomy) for those hips with minimal displacement; (4) open reduction with skeletal fixation for those hips with pronounced displacement; (5) miscellaneous methods, including traction, non-weight-bearing brace, crutches, etc. (reported in table 1).

4. Ferguson, A. B., and Howorth, M. B.: Slipping of the Upper Femoral Epiphysis: Study of Seventy Cases, J. A. M. A. 97:1867-1872 (Dec. 19) 1931.

Physical examination: Examination showed an extremely obese girl, whose physical findings were essentially within normal limits except for the left hip. The extremity lay in extreme external rotation, and any attempt at motion provoked severe muscular spasm and pain. Roentgenograms showed pronounced displacement of the head on the neck, the shadow of the neck being superimposed on the lateral margin of the acetabulum (fig. 1A).

Treatment: Within twenty-four hours the hip was manipulated with the patient under anesthesia, into what was interpreted roentgenologically as a good position. A spica held the hip in internal rotation and abduction. When the plaster spica was bivalved at the end of three months, the head showed increased density and definite evidence of aseptic necrosis (fig. 1B). The extremity was placed in counterpoised traction for several months. The increased absorption of the neck and head may be seen in roentgenograms which were taken on Feb. 11, 1932 (fig. 1C), but the head did unite to the neck.

During this period there was progressive loss in the motions of the opposite hip joint, and the joint space became thinner, although there was no evidence of

slipping of this epiphysis or other causative disease. The condition of the two joints may be seen in the roentgenogram taken on June 31, 1933 (fig. 1 D). The head on the left has been revascularized and united to the neck, although it is extremely deformed. The narrow joint space may be seen on the right, with definite irregularity in the contour of the head.

The last examination, on May 17, 1944, almost thirteen years after the original manipulation, found

her to be no longer obese. The right hip, the in which demonstrable slipping did not occur, showed only a jog of motion. The left hip showed flexion 60 degrees, and external and internal rotation 60 degrees in extension with abduction of 20 to 25 degrees and hyperextension of 20 degrees. She was able to walk without pain. She wore a 1¼ inch (3 cm) on the shoe on the side of the displaced epiphysis. Roentgenograms taken on this date showed es

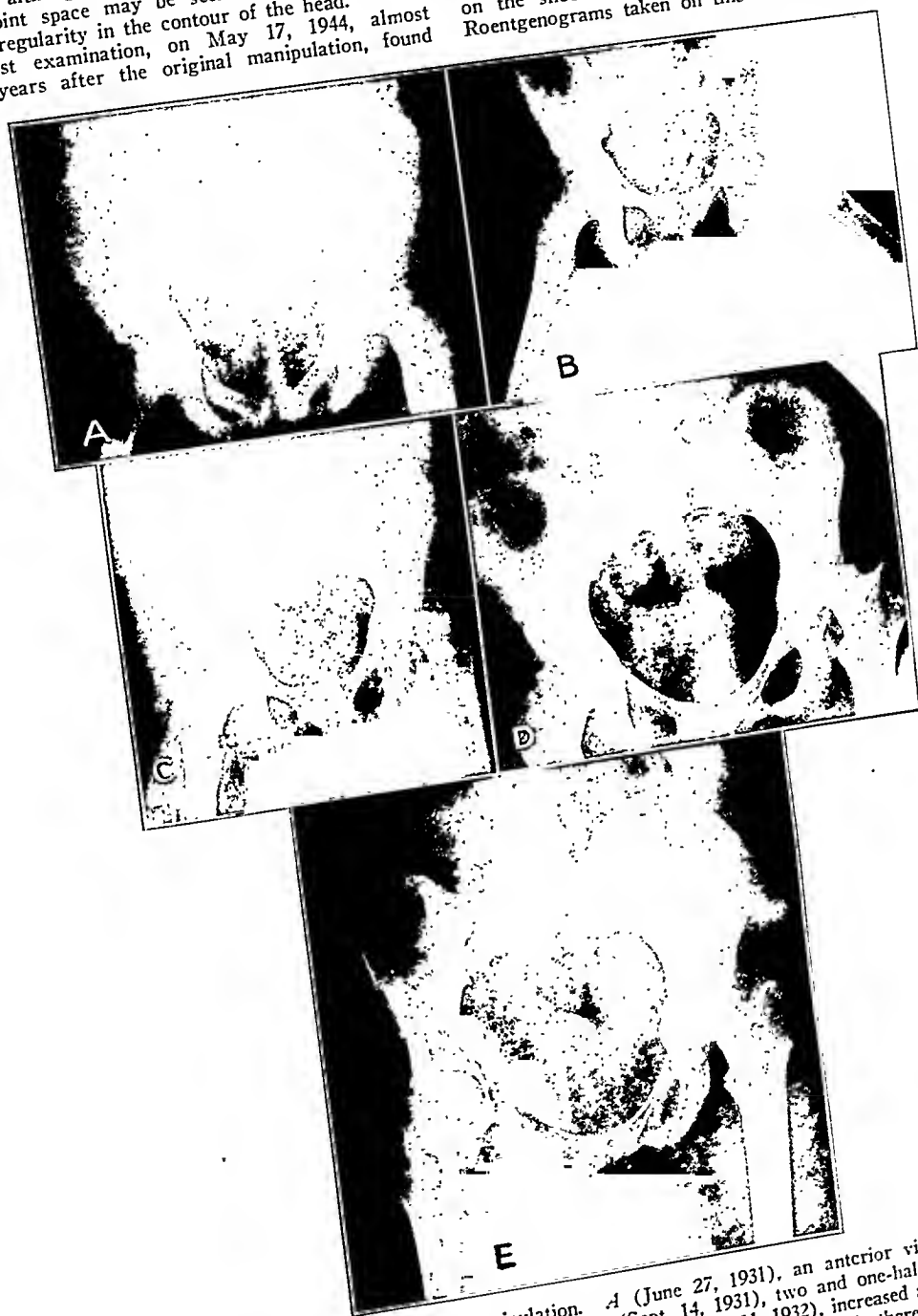


Fig. 1 (J. M.).—Treatment: closed manipulation. A (June 27, 1931), an anterior view shows essentially complete displacement of the head on the left side. B (Sept. 14, 1931), two and one-half months after closed reduction. The head is dense, and there is aseptic necrosis. C (Feb. 11, 1932), increased absorption of the head. D (June 31, 1933), the distorted head is well united and revascularized; there is a good joint space on the left. Note the narrowed joint on the right with reaction at the periphery of the head. E (May 17, 1944), the joint space on the left is about the same as eleven years before. The joint space on the right side is narrow, with tortion of the head and overgrowth of bone. There is a jog of motion only.

same contour of the head as seen eleven years ago, with distinct irregularity but with an adequate space (fig. 1 E). The right hip had an appearance which suggested the possibility of slipping of the epiphysis in the past, with decided narrowing of the joint space and formation of new bone. Serial films taken during the period when difficulty with this hip arose, however, had shown no evidence of such an occurrence. She had a shortening of 4 cm. Her result is recorded as poor.

Three hips were treated by closed reduction, with the patients under anesthesia. All 3 showed some limitation of motion, as expressed by the inefficient used. The hip of the patient just mentioned had a coefficient of 52 (normal 90 to 100). The other 2 hips treated by this method had a coefficient of 61.5 and 49.5 (table 1). In one of the hips there has been pain up to the time of writing, but 2 have caused a definite limp.

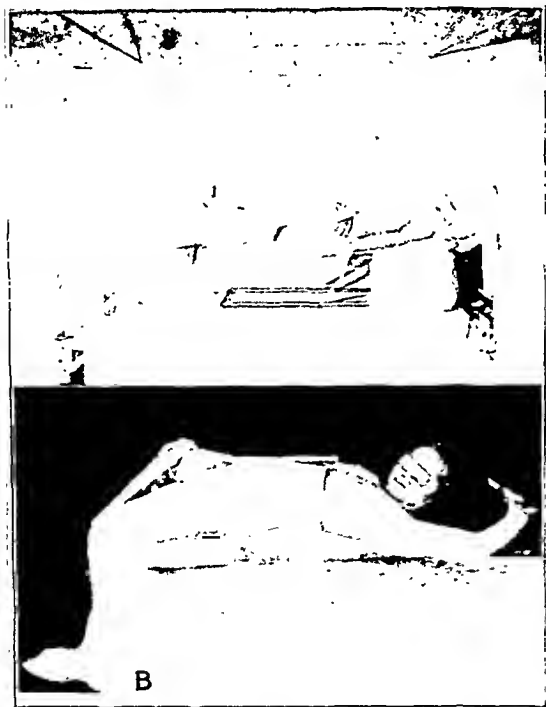


Fig. 2.—A, patient in traction, with the left hip involved. Note the internal rotation arm. The other leg is suspended to control the degree of abduction. B, patient in a spica cast, with the hip in internal rotation and abduction. The left hip is involved, and the plaster goes only to the knee on the right. The left leg is not in hyperextension as the photograph suggests.

It is anticipated in all of these hips that, judging from their roentgen appearance, further difficulty may be expected.

Traction-Spica-Traction Method.—The method takes into cognizance certain facts:

1. The blood supply to the head of the femur must not be traumatized.

2. Spasm ordinarily quiets down with traction, allowing increasing internal rotation and abduction.

3. Slipping cannot increase if the hip is immobilized in abduction and internal rotation.

4. Immobilization promotes rapid healing.

5. Immobilization in plaster with the method used has not resulted in stiff hips.

6. If the displacement is not too great, the surfaces smooth off as the process heals.

More hips were treated by this method than by any other—18 hips of 13 patients. This treatment was first used thirteen years ago. Patients ascribed as having been treated by the traction-spica-traction method followed a variation of the following routine.

Two traction forces are applied to the involved extremity: one longitudinally and the other to develop internal rotation (fig. 2 A). In practice longitudinal traction is applied through moleskin adhesive tape straps to the thigh and leg; internal rotation is accomplished by applying a wide moleskin adhesive tape strap around the thigh. This wide strap starts on the antero-lateral aspect of the thigh and passes around the medial aspect of the thigh, beneath the posterior surface and up the lateral aspect. From the junction of the posteromedial aspect on, it is faced with felt, so that it will not stick to the inferior aspect of the thigh. Overhead traction is applied to the free end. Only moderate traction is used longitudinally, usually somewhere between 5 and 10 pounds (2.3 and 4.5 Kg.), and the amount applied to the internal traction arm is evaluated as the traction is observed. Usually 5 pounds is used at the start; internal rotation must not be forced. The leg may be suspended in a Thomas splint, suspended by balanced slings or kept flat on the bed, as in Buck's extension, with the added arm for internal rotation. Traction is started in a neutral position; abduction and internal rotation are increased as tolerated comfortably. There should be no pain; the patient should be more comfortable rather than less. Traction must be started in the line of deformity. In practice the opposite leg is placed in traction and suspension so that the degree of abduction and rotation can be controlled.

As soon as spasm is relieved and the maximal degree of internal rotation and abduction obtained, the patient is placed in a hip spica (fig. 2 B). Traction is used on the average for three weeks. The essential function of the spica is to maintain the involved hip in the maximal comfortable degree of abduction and internal rotation.

This is accomplished by extending the spica to the knee on the uninvolved side and including the foot on the involved side with the knee in moderate flexion. The hip should be in slight flexion and never hyperextended. Ordinarily the patient is sent home in the spica and is readmitted to the hospital after three months. At this time the spica is removed and the condition of the epiphysial line is evaluated by roentgenograms; ordinarily there is appreciable healing at this stage.

water exercises are helpful. On occasion terbalance traction is not used, and the leg is allowed to develop motion in bed. Walking is started with crutches, not with a brace. The actual time of walking, as of all sequence of this treatment, depends on the roentgen appearance and the clinical findings.

Since the group of patients treated by this method is large and since the results are variable, the individual cases are not presented in

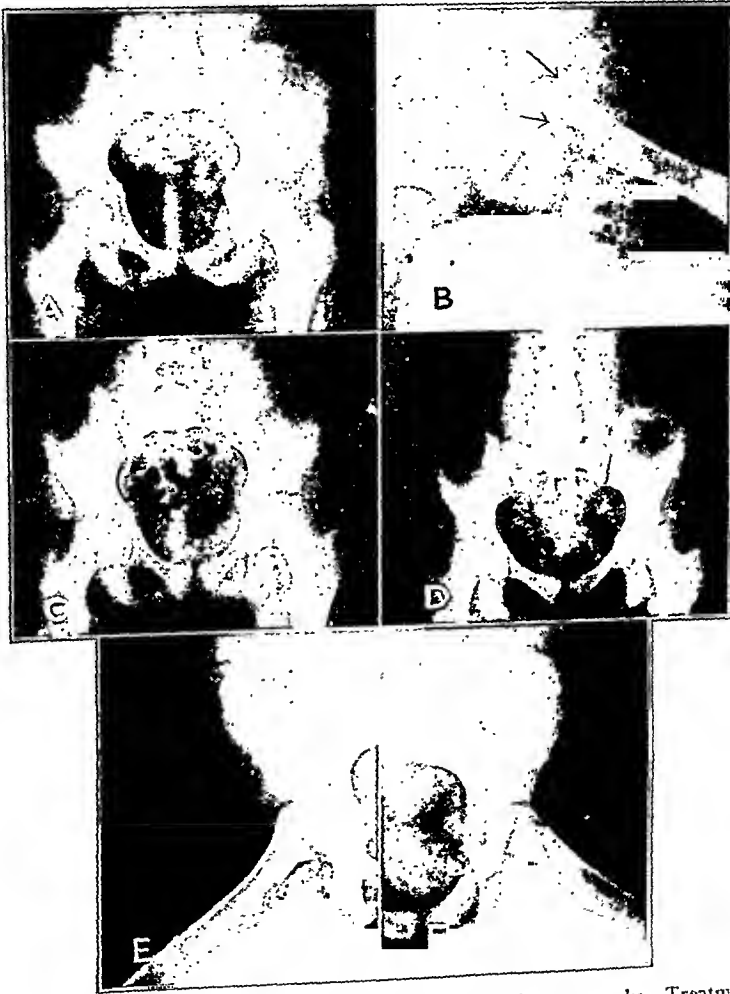


Fig. 3.—R. V., a girl 10 years of age, who had a limp on the left side for ten weeks. Treatment: traction. *A* (Sept. 5, 1941), an anterior view shows rarefaction in the metaphysal region of the left femur. *B*, the lateral projection shows 0.7 cm. of anterior displacement of the neck on the head. *C* (Dec. 1, 1941), the epiphysial line is closed on the involved side on the left. *D* (May 17, 1944), the epiphysial line is closed on the involved side on the right. *E* and *F* (May 17, 1944), lateral views of the two hips show their similarity in contour. The contour of the left hip is much better than the contour shown in *B*.

Restoration of function must be accomplished gradually. Counterpoised traction is most useful in this period. The extremity is placed in traction with a Thomas splint and a Pearson attachment and counterbalanced. The patient is encouraged to move the extremity. Under

form. A summary of the time involved in the method of therapy may be seen in table 2. A summary of results in this group of patients may be seen in table 3.

The hips treated by this technic show a variable amount of initial displacement; the

ed average was 0.8 cm., and the maximal amount was 1.5 cm.

The results in the 13 patients who had a follow-up examination after an average of six years following treatment may be classified as excellent. All patients had a normal coefficient of motion, which averaged 98.5 (90 to 110 normal) (figs. 3, 4 and 5). Flexion and abduction, motions ordinarily limited after slipped epiphysis, were normal in all, and internal rotation was normal except in 1 patient who had both hips involved; he had internal rotation of only 20

that she was immobilized in a spica for only two months. She started walking with crutches four months after the onset of symptoms and was soon allowed full activity. After a few months she started to limp but did not complain of pain. The clinician who observed her reduced her activity partially, but she returned later with a displacement of 1.5 cm., as estimated from the roentgenograms. This occurred recently, and the final result cannot be stated. This recurrent slipping should not have happened with proper supervision. The symptoms gave adequate warning of recurrent difficulty before increased displacement occurred.

TABLE 2.—Summary of the Time Involved with the Traction-Spica-Traction Method for Eighteen Hips of Thirteen Patients*

Phase of Treatment	Duration
action; average period.....	3 weeks
rest; average period.....	3½ months
counterpoised traction when used.....	1 month
walking with crutches; average period after initial treatment.....	5 months
walking unprotected; average period after initial treatment.....	7½ months
full activity; average period after initial treatment.....	11½ months

* In all cases in which the condition was bilateral but one hip was treated simultaneously, i. e., the condition was unilateral when seen.

Four hips in 3 patients who were still receiving treatment at the time of writing are not included in this table.

TABLE 3.—Results of the Traction-Spica-Traction Method in Eighteen Hips

13 hips; average follow-up period, 6 years
Average original displacement: estimated 0.8 cm.; maximal, 1.5 cm.
Coefficient of motion (Ferguson-Howorth): all normal; average 98.5 (normal 90-110)
Flexion and abduction: normal limits in all
Internal rotation: normal except for 1 patient in whom internal rotation of both hips was reduced
Pain: none
Limps: none
Increase in slipping: none
Average shortening with unilateral involvement: 1 cm.
4 hips: treatment too recent for evaluation: 1 of these had increased slipping with full activity too soon
1 hip: healing with normal motion; patient transferred to another hospital, where hip was nailed

and 10 degrees respectively at his last examination, eleven years after treatment. His hips might be placed in the good category, although he considered his hips normal in all respects. He had had maximal displacement. None of the patients had pain or limp. There was an average shortening with unilateral involvement of 1 cm.

Four hips of 3 patients in this group were treated so recently that the results could not be evaluated, but 1 of these patients should be discussed.

She was admitted at the age of 9 years and 9 months, with a two week history of pain and limp. She had minimal displacement of the head, only a few millimeters, associated with rarefaction of the neck adjacent to the epiphysis. She had the usual treatment except

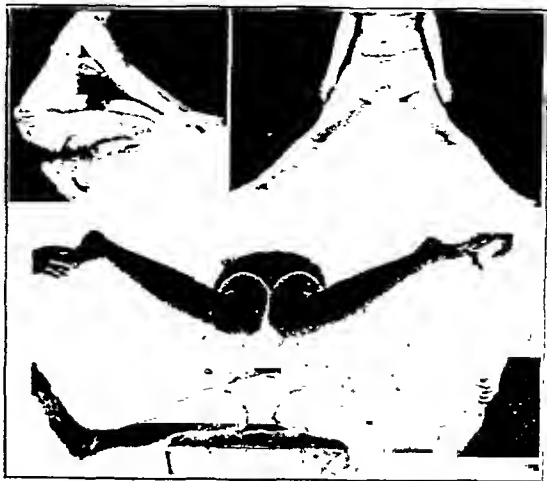


Fig. 4.—Photographs of R. V., taken on May 17, 1944, two years and eight months after slipping, show full range of action in the motions often limited after slipped epiphysis.



Fig. 5.—E. C. had slipped epiphysis on the right side seven years before, with so-called minimal displacement. The traction-spica-traction method was the treatment employed. Normal motion resulted, with no residua.

There has been no increase in the slipping in the other hips of the patients of this group, either during treatment or afterward. Instead

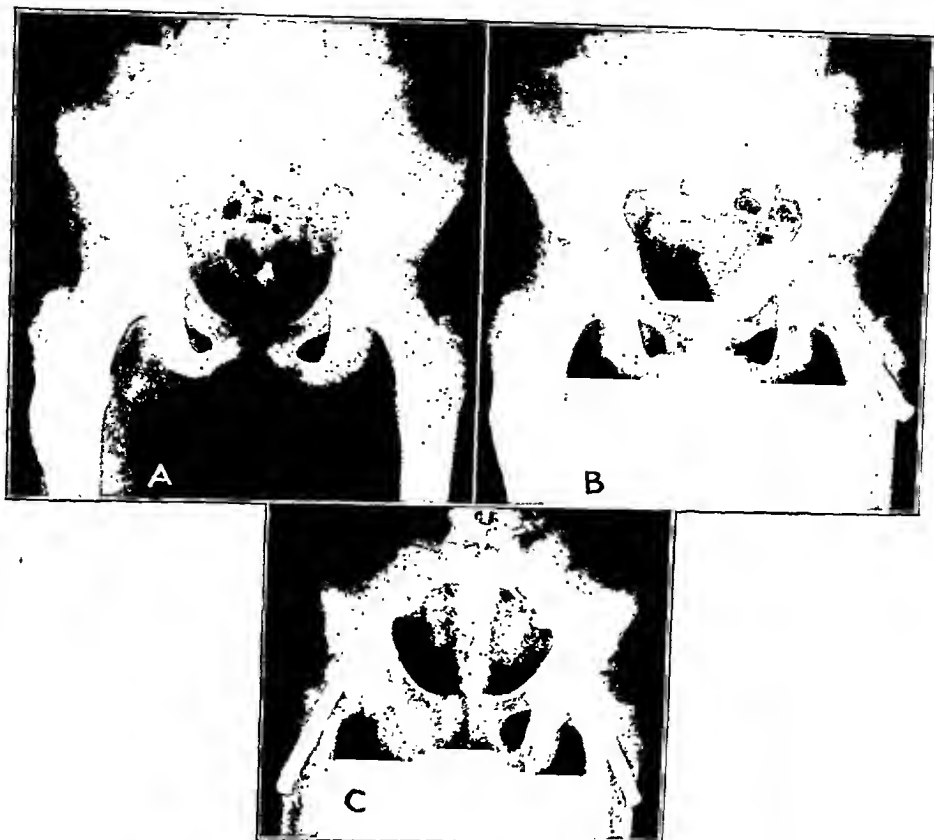


Fig. 6 (R. B.).—Minimal slipping on the right at 12 years of age and on the left one year later. Treatment, nailing in situ. *A*, eight months after the right side was nailed. Note position of the nail across the epiphyseal line. The nail is in a good position in the lateral view. *B*, six months later, after the other side was nailed. The nail is deep in position. *C*, note position of the ends of the nails five years later. Neither nail reaches site of the closed epiphyses lines. This is due to growth of the neck. The changed angle of the nail on right indicates farther slipping. This was confirmed in the lateral view.

TABLE 4.—Results of Nailing in Situ and Open Reduction with Nailing

Patient	Years Followed	Estimated Original Displacement	Index of Motion	Pain	Significant Deformity	Arthritic Change	Shortening	Limp	Result
Nailing in Situ									
A. B.	6	0.4 cm.	80.5	Rare +?	+	0	Bilateral	0	Good —
	5	0.2 cm.	84.5	0	0	0	Bilateral	0	Good
A. C.	2½	0.3 cm.	98.5	0	0	0	1.0 cm.	0	Excellent
G. N.	1½	0.5 cm.	90.0	0	0	0	0.6 cm.	0	Good +. Nail 16 where; at time of writing other hip involved
R. S.	5 mo.	0.3 cm.	Too early to evaluate
Open Reduction with Nailing									
R. B.	5½	Severe for months	23	Occasional +++	++++	Cup	2.0 cm.	+++	Poor; aseptic necrosis
D. B.	7½	Acute, complete	91.5	Rare +?	++	+?	0.7 cm.	0	Good ?
D. P.	1½	Acute, complete	100.5	0	0	0	0.6 cm.	0	Excellent
Ro. B.	6 mo.	Severe for months	93.0	Too recent to evaluate; apparently excellent

contours have improved with the healing ase (fig. 3 B and F).

The final hip in this group of patients which had not been evaluated was healing with excellent motion when the patient was transferred to another clinic for outpatient observation, since he was over age for the Children's Hospital. This hip was nailed after he was transferred. The sole reason that the epiphysial line was not completely closed.

Nailing in Situ.—Five hips with minimal displacement were treated in this manner. In each instance a large Kirschner wire was inserted as guide and a cannulated modified Smith-Petersen nail was introduced through a lateral incision without arthrotomy. In all cases the nail was in a good position.

change in the position of the nail but from growth of the neck, by which the nail was retracted from the head across the epiphysial line. This patient has on rare occasions minimal discomfort in the upper lateral part of the thigh on the involved side, but this may arise from the nail, which should be removed. The average coefficient of motion for the 4 hips was 88.4, which is just below the ascribed limit of normal, or 90. The results in the patients in this group were characterized respectively as excellent, good + good and good — (figs. 7 and 8).

Open Reduction with Skeletal Fixation.—Four hips were treated by open reduction with nailing; in all the displacement was severe (table 4). The results in the patients of this group were determined after an average of four

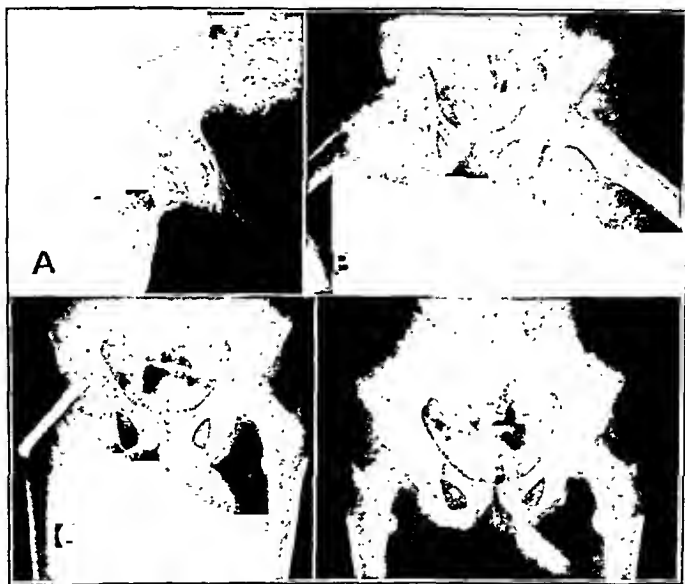


Fig. 7.—A. C., a boy of 14 years with pain and limp on the right side for five months. Treatment: lateral nailing in situ without arthrotomy. A (Nov. 10, 1941), an anteroposterior view shows changes in the neck adjacent to the epiphysis. B (November 10), a semilateral view shows an anterior displacement of the neck of about 4 mm. C (May 6, 1942), six months after nailing: The nail is in position. The epiphysial line is narrower on the right. D (May 3, 1942), two and one-half years after nailing: The nail was removed when the line had become obliterated, ten months after nailing. The neck is broader than normal. The line of the nail is still visible.

The results in the 4 hips which were evaluated after an average of four and eight-tenths years following the nailing were good (the fifth hip was nailed too recently for evaluation), but neither in the contour of the hips nor in motion were they as good as those after treatment with the traction-spica-traction method (table 4). Two hips (of 1 patient) had a coefficient of motion below 90, namely 80.5 and 84.5. In 1 of these hips, which was fixed with the nail in excellent position deep in the head, an increase in displacement of the head on the neck developed subsequently (fig. 6). This arose not from a

and eight-tenths years. In 2 the original displacement was acute and essentially complete; in the other 2 the displacement was of several months' duration. In 1 patient, R. B., aseptic necrosis developed postoperatively and the result was poor. The second patient in this group, D. B., although her hip had a normal coefficient of motion and may be described as good at the time of writing, had after operation some changes in the head of the femur, which now has minimal irregularity in contour.

The last 2 patients in the open reduction group, D. P. and R. B., had reduction of the dis-

placement with a variation in technic, which I believe is important. In these patients, the circulation of the head was perfectly maintained. One of the hips, which has been observed sufficiently long to evaluate, has normal function in all respects; the other, although it is too soon to assess the result, has excellent function at the time of writing.

The operation as performed recognizes the importance of the posteroinferior cervical vessels particularly the vessels in the retinacula of Weitbrecht, in maintaining the circulation of the head and the importance not only of not cutting them but of not stretching them so as to interfere with their lumens. It recognizes, as pointed out elsewhere, that since the head in slipped epiphysis has usually been in a posterior-inferior position for some time, with resultant shortening of these

accomplished with an osteotome and a hammer. In the healing phase, this bone may be left. The periosteum and the retinacula on the posterior inferior aspect must not be cut or traumatized.

Once the neck has been cut across, a sufficient section of the neck is removed to allow the head to be placed in position without stretching or twisting the periosteum and the retinacula (figs. 9D and E). The shape of the section removed varies with the deformity and should be designed to restore the normal angle of the neck and head. If the slipping is recent, the line of osteotomy is essentially parallel to the "fracture surface" of the neck. If the slipping is of some

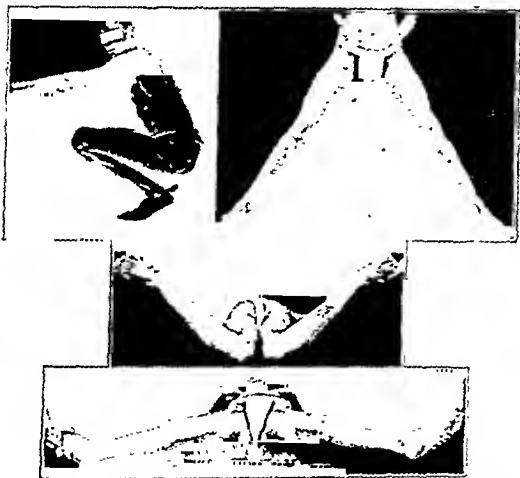


Fig. 8.—Clinical photographs of A. C. taken in June 1944, showing excellent range in motions frequently limited in slipped epiphysis. Rating: excellent.

vessels and the surrounding soft tissues, reduction of the head by prying it into position compromises the blood supply to the head from this source (figs. 9A and B).

The operation has the following essential features. On exposure of the neck of the femur, a longitudinal incision is made in the periosteum on the anterior aspect of the neck with a transverse prolongation over the anterior and lateral aspect of the proximal end of the neck. The periosteum is carefully stripped from the neck with a curved elevator, with preservation of the periosteum and retinacula on the inferior-posterior aspect (fig. 9C).

At this stage, if the displacement is fresh, the soft osteoid may be separated with little effort and the proximal end of the neck exposed. If the connection is more firm, separation is

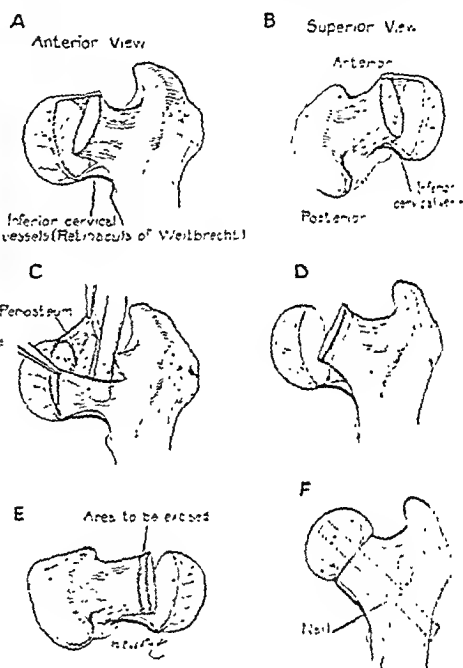


Fig. 9.—Diagrammatic drawings. A and B, anterior and superior view respectively of the head and neck of the femur in slipped epiphysis, showing the direction of displacement of the head. The neck rotates laterally and comes to occupy a superior and anterior position and the head comes to occupy an inferior and posterior position. The apparent space between the head and neck does not exist. The inferior cervical vessels in the retinacula of Weitbrecht may be seen supplying the head. C, the periosteum is being elevated, to protect the retinacular vessels. D and E, diagram showing bone excised from the neck to allow replacement of the head without tension on the retinacular vessels. The amount of bone excised varies with the condition. F, the head is replaced with skeletal fixation; the vessels are

duration and there is formation of new bone. If it is necessary to remove more bone superiorly and anteriorly. The head is then fixed in position in the usual manner, with skeletal fixation (fig. 9F). If the process is healed at the

osteotomy, there is no reason why osteotomy should not be done, a little way removed from site of the epiphysial line. This makes fixation more simple, but the osteotomy should not be done too far distally, for it will interfere with the circulation of the head.

of extreme pain in the left hip following a fall. She had had some discomfort in this hip eight months before, but this had subsided.

Physical Examination: Examination revealed an obese girl in obvious pain; the hip was held in external rotation of 45 degrees, with severe muscular spasm and pain on any motion. Roentgenograms showed es-



Fig. 10 (D. P.).—Treatment: open reduction with nailing. *A* (March 27, 1943), anteroposterior view shows complete displacement on the left. *B* (May 20, 1944), the bone is well united with the nail in position. *C* (May 20, 1944), lateral view shows excellent contour.

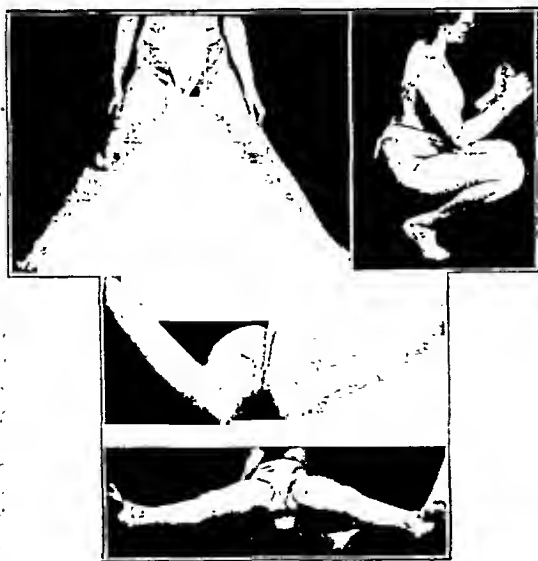


Fig. 11.—Clinical photographs of D. P. taken one year after operation. Motion is normal.

The hips treated by this method have a coefficient of motion of 100.5 and 93.0. The history of 1 of the patients in this group is included.

D. P., a girl aged 11 years and 10 months, was admitted to the hospital on March 29, 1943, complaining

essentially complete displacement of the head on the neck (fig. 10 *A*).

Treatment: The day after her admission to the hospital, operation was performed, with resection of enough of the proximal neck of the femur to allow reduction without stress on the retinacular vessels. Fixation was accomplished with a nail. Postoperatively the patient was kept in traction for six weeks, with increasing motion. She was not allowed to walk with partial weight bearing using crutches until June 15, and only after six months following the operation was she allowed activity without crutches.

Follow-Up Examination: One year and two months later examination disclosed painless function, normal in all respects (fig. 11). Roentgen examination on May 20, 1944 showed the nail in position and good contour of the hip (fig. 10 *B* and *C*).

COMMENT ON TREATMENT

The final evaluation of the results of treatment in this disease depends on the lifetime experience of the patient. The head of the femur is so peculiarly subject to degenerative changes in late adult life that what may appear to be a good hip at 25 years of age has the possibility of acquiring secondary changes which would place it in the poor category at a later age. A study of fifty-year end results would give the answer.

The best results were obtained with the traction-spica-traction method and the next best

results with the nailing in situ method without arthrotomy. The results in these two groups were comparable except for the paucity of patients whose hips were nailed. However, the results which I obtained with nailing in situ were essentially the same as those reported by Klein, Joplin and Reidy⁵ in a larger number of patients treated by this method.

In this series the hips nailed in situ had less average initial displacement than those treated by the traction-spica-traction method, 0.4 compared with 0.8 cm.

In the follow-up study the average coefficient of motion in those hips treated by the traction-spica-traction method was 98.5; that in those nailed was 88.4. The only patient in the two groups who had discomfort referable to the hips was 1 whose hip had been nailed. This was probably due to the head of the nail. The nail had not been removed.

The evidence would suggest that either the traction-spica-traction method or the nailing in situ method is satisfactory for slipped epiphysis with minimal displacement and that in addition the traction-spica-traction method is effective for those hips with moderate displacement up to an estimated amount of 1.5 cm.

Proponents of the nailing method would point out that with this method the stay in the hospital is short, the time that the patient must be protected is brief and there is no worry about further slipping. The disease, however, is frequently bilateral, and after nailing followed by full activity involvement of the other side is common. In 2 of the 5 hips in this series which were treated by nailing in situ and in 3 of the 11 reported by Klein and co-workers, slipping occurred on the opposite side after nailing. Furthermore, in 1 of the hips which was well nailed according to all criteria, further slipping occurred, despite the presence of a nail. This arose from growth of the neck, which carried the nail distally across the epiphysal line. The result in another hip treated by this method corroborated the fact that growth may occur with the nail extending across the epiphysal line, as shown in certain experimental work.⁶

The advantage of the traction-spica-traction method is that the results so far seem to be better than those obtained by other methods. The contention that further slipping may occur with the hip in traction and that stiffness is induced by fixation in a plaster spica is not validated by my

experience.⁷ Further displacement cannot if internal rotation is maintained.

Criticisms of the method are that it requires longer care and hospitalization, that the ability during the treatment phase is less, and that the possibility of recurrent slipping until the epiphysal line is obliterated may cause the line to heal prematurely after slipping and it has in most instances healed properly after treatment. Once the healing phase is reached, further progress of the process can be accurately evaluated by history, clinical and roentgenography.

In only 1 of 18 hips which were treated by the spica-traction-spica method was there a recurrent slipping. Recurrence occurred after a period of immobilization while the patient, a 10 years of age, was observing full activity. The clinician had adequate warning of difficulty evidenced by a recurrent limp some time before the slipping occurred. This patient, though the process is too recent to evaluate, gives no indication that a good result will be obtained despite the recurrence of slipping.

Increased slipping has not occurred in other hips for which this method was used. It has been found instead that the contour improvement probably not by any reduction of the displacement of the head but rather through growth adaptive factors.

The limited activity which patients in this group need to follow for a period is probably helpful in preventing involvement of the second side. In only 1 instance did slipping epiphysis occur on the opposite side after treatment by this method, and this was nearly three years after the initial side was affected.

In an attempt to decide whether a hip should be treated by nailing or by the traction method many considerations arise of these factors may be listed: the facilities available for therapy; the experience of the physician who will carry on the treatment, and the closeness with which the activities of the patient can be controlled. Treatment by the traction method demands effective control of this group of patients there was little difficulty with this score, although most of them were from a public ward. Certainly harm can occur in the nailing of hips by men who are not properly prepared to perform the procedure. On the other hand, the traction-spica-traction method must be handled properly too. One patient in this group

5. Klein, A.; Joplin, R. J., and Reidy, J. A.: Treatment in Cases of Slipped Capital Femoral Epiphysis at the Massachusetts Hospital, *Arch. Surg.* 46:681-686 (May) 1943.

6. Green, W. T., and Harris, L.: Unpublished data.

7. Mayer, L.: The Importance of Early Diagnosis in the Treatment of Slipped Femoral Epiphysis, *J. Bone & Joint Surg.* 19:1045-1051, 1937. Wilson, P. D.: Treatment of Slipping of the Upper Femoral Epiphysis with Minimal Displacement, *Ibid.* 20:370-376, 1938.

example, had slightly increased hyperextension of the knee on the involved side, which was from faulty application of a plaster spica.

The final criterion in choosing between the methods will depend on how the hips stand up in the future. Is the better function of the hips which have been treated by the traction-spica-traction method pertinent to their future progress? Is the slightly lessened function of the hips which have been nailed significant? Certainly the hips nailed are good at the time. At the question arises as to whether they will be as good in the future.

It is possible that the results obtained from nailing in situ might be improved by preliminary traction if there is any degree of spasm, by skeletal fixation using a less traumatic method and by protecting the hip longer in the postoperative period.

For patients with extreme acute displacement the indication for open reduction with skeletal fixation seems real. Although my experience is so limited for conclusions to be drawn, it would seem that preservation of the retinacular vessels and excision of enough of the neck to allow replacement without strangulation of these vessels should obviate or at least greatly decrease the incidence of aseptic necrosis of the head of the femur.

The same technic applied to a hip which has healed with extreme displacement gives promise of being equally good, although the technical difficulties are much greater in this stage.

Unanswered is the question as to just how much displacement warrants an open procedure. One patient with the heads equally displaced to an amount estimated as 1.5 cm. had excellent function eleven years after treatment with the traction-spica-traction method. Whether it will be good after fifty years is the question. At the present time any displacement over 1.5 cm. is considered as warranting an open procedure. This is subject to revision, however.

My experience with closed reduction may be added to other evidence against this method. With such a manipulation there is a likely possibility of interrupting the retinacular vessels and producing aseptic necrosis. This does not mean that on occasion with acute displacement gentle reduction may not produce a good hip.

The use of a walking brace for 1 of the patients was followed by slipping on the other side.

It is suggested that in certain cases no matter what the treatment the result may be bad.

One of the patients, B. S., reported in the group of patients receiving miscellaneous treatment, had on admission to the hospital involvement of both sides, with

a history of symptoms on one side for fourteen months and on the other for seven months. She had severe muscular spasm and protected both hips with greatly limited motion, and the one involved for the longest period was practically fixed. Roentgenograms showed what was interpreted as 1.5 cm. displacement on the two sides with pronounced narrowing of the joint on the one side and moderate narrowing on the other.

Despite traction for five months, the worse side remained practically immobile, and subsequent exploration at the time of arthroplasty showed almost complete degeneration of the joint. At no time was the head dense, which indicated aseptic necrosis.

Did this degenerative process arise solely from traumatic arthritis? It seems that in certain instances there is some factor other than interference with circulation to the head of the femur and traumatic arthritis which influences the result in slipped epiphysis.

I have had no experience with drilling or with subtrochanteric osteotomy for slipped epiphysis. If drilling is done I believe it should be accompanied by skeletal fixation. Subtrochanteric osteotomy is an unanatomic makeshift procedure, but it may have its place in certain cases in which the head has healed in a deformed position.

SUMMARY

In a consecutive series of 26 patients with slipped upper femoral epiphysis in 36 hips, the results in 28 of the hips have been assessed after an average of six and three-tenths years.

In 10 patients the condition was bilateral.

Early diagnosis before significant displacement occurs is the key to the problem.

In adolescence limp with pain in the hip, thigh or knee, which is often intermittent at the start, is suggestive, particularly if the child is obese.

Reduced internal rotation, abduction and flexion of the hip with pain and spasm in the extremes of these motions are early physical findings.

Early roentgen findings are rarefaction in the metaphysial region and anterior displacement of the neck on the head, as seen in the lateral view.

Various methods of treatment, which are assessed in this report, include the following: (a) In those hips with minimal to moderate displacement the best results were obtained by a method using a particular combination of traction and plaster fixation. (b) In hips with minimal displacement nailing in situ without arthrotomy gave good results. (c) In those hips with severe displacement, open reduction with skeletal fixation gave good results provided certain technical criteria, which are described, were met. (d) Closed manipulative reduction did not seem to be a good method.

All satisfactory methods of treatment consider the mechanism of displacement and maintain the circulation to the head of the femur.

If the patient is obese, reduction of weight is helpful in the treatment.

The final evaluation of the results in slipped epiphysis depends on the adult experience of the patients.

ABSTRACT OF DISCUSSION

DR. FREMONT A. CHANDLER, Chicago: Dr. Green's presentation of slipped femoral epiphysis brings into sharp focus a clinical entity that has become blurred by the rapid swing of therapy from conservative treatment to radical operation and back again. The approach to cases of slipped femoral epiphysis should be individual and the procedures adapted to the need of each case. The duration and degree of the deformity as well as the condition of the epiphyseal plate will determine the outcome.

If reduction and fixation can be accomplished by gentle means, such should prevail. Capsular and vascular changes will be minimal and function of the joint preserved. However, if the deformity is older and more fixed, manipulation will only add insult to the already changed joint.

Correction by osteotomy of the neck of the subtrochanteric area is in order. Surgical damage to the circulation of the epiphysis must be avoided. This means that the soft structures along the posterior aspect of the femoral neck should not be overstretched or divided. Cuneiform osteotomy distal to the epiphyseal line accomplishes reduction with the least trauma.

Fixation by position with the hip in a plaster splint or, better still, some form of internal fixation is necessary.

I find nothing to disagree with and I approve wholeheartedly of Dr. Green's presentation.

I should like to inquire as to the duration of traction following open reduction in Dr. Green's older cases. When is weight-bearing activity permitted in the group of older cases? From his description I gathered it was about ten months. I should like to have him emphasize that. What are the exercises which he advocates for this particular group of cases? He might clarify them a bit by describing them briefly.

This is a timely paper. The condition is being encountered right along, and the results have not been as satisfactory as they should have been.

DR. WALTER P. BLOUNT, Milwaukee: This is a controversial subject because the results are so variable. In some cases, with little or no treatment the results are brilliant. In others, with the most energetic treatment the results are catastrophic. For this reason the study of any small series of cases is almost valueless. This is one of the best collections of cases that I have seen, and its analysis is praiseworthy.

The treatment as outlined in the first part of the discussion is probably the best for the physician who is not expert in surgical operations on the hip or who has not the facilities for the more radical procedures. I admit that it is not ideal, from either a medical or a surgical standpoint and certainly not from an economic one. Among the early cases in which treatment was conservative I saw some disasters. The last slipped femoral epiphysis which I treated by traction and a cast became stiff in severe deformity. I think that this ankylosis was inevitable. I am glad that I did not operate.

My friends who were using the flanged nail for internal fixation of incompletely slipped heads which did

not need reduction or incompletely slipped heads which had such bad results influenced in subsequent cases to use another fixation, with the smaller Moore nails. More adaptable in the treatment of various of the hip. In slipped femoral epiphysis, nails or screws are superior to the single nail. The reason is that in this condition the surface, which seems so soft in the roentgen, is actually so hard that it is difficult to drill through it. The most satisfactory procedure is pointed nails or screws across the line. The minimum of trauma.

DR. J. WARREN WHITE, Greenville, S. C. particularly to emphasize the value of traction case which I observed what looked like a coxa vara was really a gradually developed or a slow slipping of the epiphysis.

This case is representative of a series of the behavior of the hip was exactly alike. strength the epiphysis was wrenched off, traction with about 25 to 30 pounds (11 to 14 lbs.) been used for a month, the head could be into a fairly satisfactory position.

And I can prove that all the blood supply was not ruined. Constant traction over weeks pulled out the capsular cuff so that tissue through which enough vessels passed to head in good condition.

Four and a half years afterward the child is presented here was still perfectly normal. year end result will be interesting, but I have this case simply to emphasize what I feel is a tremendously important point, that is, maintenance of traction over a long period, at least during convalescence.

DR. WILLIAM T. GREEN, Boston: Dr. Chandler about the use of traction after open reduction. Since I am concerned about the circulation of the femur, I have made every effort to fix patients after open reduction and have them in traction about six weeks after operation, starting while they were still in traction. In general allowed weight bearing with crutches at the three months—that is, partial weight bearing motions and use of the leg in about three months full weight bearing in six months.

If there is evidence of aseptic necrosis in early cases, of course the follow-up period is long, and such changes should be recognized in inception—that is, before the head is crushed—before necrosis exists.

Patients treated by the traction-spica-traction are allowed to walk with crutches on an average five months after the treatment is started. The interval for weight bearing without crutches is seven and one-half months, with full activity on an average of eleven and one-half months. All dates date from the start of treatment.

Dr. Chandler asked the purpose of the exercises the removal of the spica for those patients treated by the traction-spica-traction method. They are done to increase motion in the hip joint, to develop the gluteus maximus and the abductor muscles of the hip and secondarily to promote calcification in the involved area. The exercises are active, not passive. Traction which is counterpoised allows active motion and is an excellent way to start early activity. Underwater exercises may be used if convenient.

Dr. Blount mentioned 1 patient who did badly. occasion it would seem that an unknown factor entered into the prognosis. Incidentally, a hip which does not loosen up with traction should not be placed in a spica.

r. Blount mentioned the economic consideration involved in the longer period of hospitalization demanded by the traction-spica-traction method. The period of hospitalization is much reduced by the fact that in practice the period in which the patient is in the spica is primarily spent at home. This treatment takes longer, if the results are better the increased time is justified.

As regards the use of skeletal fixation for those hips with minimal displacement, I think it would be well if patients have spasm first to institute traction including internal rotation until the muscular spasm is eviated or minimal. It is true that skeletal fixation methods other than the flanged nail may be less automatic. I believe too that partial weight bearing

with crutches for a considerable period after the fixation is desirable and may improve the result in these hips. The results in the hips with minimal displacement which were treated by skeletal fixation have been good; but at this time they do not seem quite as good as those treated by the traction-spica-traction method. The final evaluation, however, must depend on the comparative lifetime performance of the hips.

Dr. White's case is most interesting. I believe that if one proposes to change the position of the head the use of traction with internal rotation is much less likely to produce aseptic necrosis than is manipulation with the patient under anesthesia. It is well to recall that the result in any case may be good in spite of the treatment.

EVALUATION OF GELATIN AND PECTIN SOLUTIONS AS SUBSTITUTES FOR PLASMA IN THE TREATMENT OF SHOCK

HISTOLOGIC CHANGES PRODUCED IN HUMAN BEINGS

CAPTAIN HANS POPPER* AND LIEUTENANT BRUNO W. VOLK
MEDICAL CORPS, ARMY OF THE UNITED STATES

KARL A. MEYER, M.D., AND DONALD D. KOZOLL, M.D.†
CHICAGO

AND

LIEUTENANT COMMANDER FREDERICK STEIGMANN (MC), U.S.N.R.§

A substitute for plasma in the treatment of shock ideally should increase the reduced blood volume without producing significant untoward effects. Only the presence of large molecules which retain the injected fluid within the circulation produces a sustained rise of the blood volume. Such hydrophilic colloidal solutions have been observed to produce undesirable side effects; therefore, these side effects should be evaluated before the solutions are used as plasma substitutes.

Increase of the blood volume with solutions devoid of red cells reduces the red cell concentration, as measured by the hemoglobin concentration or the hematocrit value. Hemodilution is easily recognized by simple laboratory methods, which are sufficiently accurate for clinical evaluation to substitute for the elaborate methods for determination of the blood volume. The production of hemodilution then can be used as a criterion for the efficiency of a plasma substitute in the treatment of shock.

Among the undesirable effects of macromolecular substances pseudoagglutination of erythrocytes, as recognized by rouleau formation¹ and rise in the sedimentation rate, has

been observed and reported.² Recently, Hueper described a "hematologic" reaction due to intravenous administration of macromolecular substances; it is characterized by anemia, leukopenia or leukocytosis, impairment of coagulation, thrombopenia, hemorrhagic diathesis and decrease in agglutination and sedimentation rate of erythrocytes. A second important reaction is that of the tissues, chiefly as the result of deposition of macromolecular substances in the organs. Acacia (used as a plasma substitute in the first World War and more recently in the treatment of nephrosis) was found deposited in the liver. Hueper³ saw characteristic changes after the administration of other macromolecular substances as well.

To these criteria should be added the therapeutic results on patients in shock, the occurrence of pyrogenic and other clinical reactions, the problem of antigenicity, the effect on the function of the liver and kidneys and the results of experiments on animals, especially of those

2. Ivy, A. C.; Greengard, H.; Stein, I. F., Jr.; Grodins, F. S., and Dutton, D. F.: The Effect of Various Blood Substitutes in Resuscitation After an Otherwise Fatal Hemorrhage, *Surg., Gynec. & Obst.* 76:85, 1943.

3. Hueper, W. C.: Macromolecular Substances as Pathogenic Agents, *Arch. Path.* 33:267 (Feb.) 1942.

4. Andersch, N., and Gibson, R. B.: Studies on Effects of Intravenous Injections of Colloids, Deposition of Acacia in Liver and Other Organs and Its Excretion in Urine and Bile, *J. Pharmacol. & Exper. Therap.* 52:390, 1934. Kendrick, A. B.; Keeton, R. W., and Foley, E. F.: Immediate and Delayed Disposal of Acacia Injected Intravenously in Dogs, *Proc. Soc. Exper. Biol. & Med.* 39:465, 1938.

5. (a) Hueper, W. C.: Experimental Studies in Cardiovascular Pathology: Pectin Atheromatosis and Thesauritis in Rabbits and in Dogs, *Arch. Path.* 31:883 (Nov.) 1942; (b) Experimental Studies in Cardiovascular Pathology: Effects of Intravenous Injections of Solutions in Gum Arabic, Egg Albumin and Gelatin upon Blood and Organs of Dogs and Rabbits, *Am. J. Path.* 18:895, 1942.

* Director of Laboratories of Cook County Hospital and of the Hektoen Institute for Medical Research, on leave of absence.

† Abbott Fellow, Department of Surgery, Northwestern University Medical School.

§ Director of Department of Therapeutics, Cook County Hospital, on leave of absence.

From the Hektoen Institute for Medical Research and the Departments of Surgery and Therapeutics, Cook County Hospital.

This work was supported by grants from the Upjohn Company, Kalamazoo, Mich., and from the California Fruit Growers Exchange, Ontario, Calif.

Presented at the Seventeenth Annual Meeting of the Central Society for Clinical Research, Nov. 3, 1944, Chicago.

1. Hanzlik, P. J., and Karsner, H.: Anaphylactoid Phenomena from Intravenous Administration of Various Colloids, Arsenicals and Other Agents, *J. Pharmacol. & Exper. Therap.* 14:379, 1920.

ling with shock due to hemorrhage, trauma burn.

In the past years extensive work along these lines has been performed on isinglass,⁶ gelatin⁷

6. (a) Taylor, N. B., and Water, E. T.: Isinglass Transfusion Fluid in Hemorrhage, *Canad. M. A. J.* 547, 1941. (b) Taylor, N. B., and Moorhouse, S.: The Use of Isinglass as a Blood Substitute in Hemorrhage and Shock, *ibid.* 49:251, 1943. (c) Pugsley, H. E., and Farquharson, R. F.: The Clinical Use of Isinglass, *ibid.* 49:262, 1943.

7. (a) Bayliss, W. M.: The Use of Gum Solutions in Intravenous Injections, *Brit. M. J.* 1:564, 1917. (b) Hogan, J. J.: The Intravenous Use of Colloidal (Gelatin) Solutions in Shock, *J. A. M. A.* 64:721 (Feb. 1915). (c) Gordon, H.; Hoge, H. J., and Lawson, J.: Gelatin as Substitute for Blood After Experimental Hemorrhage, *Am. J. M. Sc.* 204:4, 1942. (d) Lawson, J.: The Measurement of Bleeding Volume in the Dog or Studies on Blood Substitutes, *Am. J. Physiol.* 140:20, 1943. (e) Lawson, H., and Rehm, W. S.: The Relative Value of Various Fluids in Replacement of Blood Lost by Hemorrhage, with Special Reference to the Value of Gelatin Solutions, *ibid.* 140:431, 1943. (f) Parkins, W. M.; Koop, C. E.; Riegel, C.; Vars, I. M., and Lockwood, J. S.: Gelatin as a Plasma Substitute, with Particular Reference to Experimental Hemorrhage and Burn Shock, *Ann. Surg.* 118:193, 1943. (g) Little, M. J., and Wells, H. S.: Capillary Permeability to Intravenously Administered Gelatin, *Am. J. Physiol.* 138:495, 1943. (h) Little, J. M., and Jameron, J. T.: Plasma Retention, Urinary Excretion and Effect upon Circulating Total Red Cell Volume of Intravenous Gelatin in Normal Dogs, *ibid.* 139:438, 1943. (i) Plasma Retention, Urinary Excretion and Effect upon Circulating Total Red Cell Volume of Intravenous Gelatin in Dogs with Diminished Volume, *ibid.* 140:636, 1944. (j) Grodin, F. C.: Gelatin as a Blood Substitute in Shock Due to Limb Trauma, *Federation Proc.* 2:17, 1943. (k) Janota, M.; Necheles, H.; Weston, R. E.; Weisman, V., and Levinson, S. O.: Gelatin Infusion in Hemorrhagic Shock, *Exper. Med. & Surg.* 1:298, 1943. (l) Kleinberg, W.; Remington, J. W.; Eversole, W. J.; Overman, R. R., and Swingle, W. W.: The Effectiveness of Plasma, Gelatin and Saline Transfusions in Preventing Shock Induced by Leg Muscle Trauma and Tourniquets, *Am. J. Physiol.* 140:197, 1943. (m) Brunschwig, A.; Scott, V. B.; Corbin, N., and Moe, R.: Observations on the Intravenous Injection of Gelatin for Nutritional Purposes, *Proc. Soc. Exper. Biol. & Med.* 52:46, 1943. (n) Brunschwig, A.; Corbin, N., and Johnston, C. D.: Intravenous Gelatin, *Ann. Surg.* 118:1058, 1943. (o) Kozoll, D. D.; Popper, H.; Steigmann, F., and Volk, B. W.: Use of Gelatin Solutions in the Treatment of Shock, *Am. J. M. Sc.* 208:141, 1944. (p) Ely, J. O., and Angulo, A. W.: Experimental Burns: The Influence of a Gelatin-Glucose-Salt Solution on the Hemoglobin Concentration of Burns, *J. Franklin Inst.* 235:197, 1943. (q) Scott, C. C.; Worth, H. M., and Robbins, L. B.: Comparative Value of Some Blood Substitutes Used for Treatment of Experimental Shock, *Arch. Surg.* 48:315 (April) 1944. (r) Koop, C. E.; Fletcher, A. G.; Riegel, C., and Lockwood, J. S.: Gelatin as a Plasma Substitute, *Surgery* 15:839, 1944. (s) Swingle, W. W.; Kleinberg, W., and Hays, H. W.: A Study of Gelatin and Saline as a Plasma Substitute, *Am. J. Physiol.* 141:329, 1944. (t) Swingle, W. W., and Kleinberg, W.: Plasma, Gelatin and Saline Therapy in Experi-

and Pectin.⁸ In the Hektoen Institute investigations with the administration of pectin and gelatin solutions to patients in shock and to hospital control subjects were conducted, and the impression was gained that the two solutions are equally effective in the treatment of shock.⁹ For a reliable comparison between the solutions—which is the object of this presentation—data on hemodilution, pseudoagglutination of erythrocytes (as an example of the hematologic alterations) and tissue changes were selected from a variety of studies, which have been partly reported elsewhere.¹⁰

MATERIAL AND METHODS

The studies are based on experience with the intravenous administration of 257 liters of gelatin solution to 162 patients in 213 individual infusions; the quantity of solution administered ranged from a total of 1 to 10 liters per patient. Pectin solution was administered in the amount of 235 liters to 155 patients in 251 individual infusions, for a total of from 1 to 9 liters per patient. About half of the patients were hospital control subjects; the other half were patients with various degrees of surgical, traumatic, hemorrhagic and medical shock. The clinical details have been discussed elsewhere.¹¹ For these patients the concentration of hemoglobin (determined by a photoelectric colorimeter), the hematocrit value and the sedimentation rate of the red cells (both measured by the Wintrobe tube) were determined before, immediately after and twenty-four hours after the infusions. The mean corpuscular hemoglobin concentration was calculated according to the equation of Wintrobe.¹² The percentage change in the hemoglobin concentration, hematocrit value and mean corpuscular hemoglobin concentration, determined before

mental Wound Shock, *ibid.* 141:713, 1944. (u) Ivy and others.²

8. (a) Hartman, F. W.; Schelling, V.; Harkins, H. N., and Brush, B.: Pectin Solution as Blood Substitute, *Ann. Surg.* 114:212, 1941. (b) Hartman, F. W.; Schelling, V.; Brush, B., and Warren, K. W.: The Relative Value of Pectin Solution in Shock, *J. A. M. A.* 121:1337 (April 24) 1943. (c) Jacobson, S. D., and Smyth, C. J.: Plasma Volume Changes Following the Intravenous Injection of Pectin and Physiologic Saline in Man, *Proc. Soc. Exper. Biol. & Med.* 50:218, 1942. (d) Middleton, S., and Wigger, C. J.: Some Effects of Pectin Solutions During Post-Hemorrhagic Hypotension, *Am. J. Physiol.* 140:326, 1943. (e) Kozoll, D. D.; Steigmann, F., and Popper, H.: Studies of Pectin Administration to Patients Not in Shock, *Proc. Soc. Exper. Biol. & Med.* 53:66, 1943. (f) Meyer, K. A.; Kozoll, D. D.; Popper, H., and Steigmann, F.: Protein Deficiency in Surgical Patients, *Surg., Gynec. & Obst.* 78:327, 1944. (g) Figueroa, L., and Lavieri, F. J.: The Use of Pectin and Other Agents to Prevent Shock, *Surg., Gynec. & Obst.* 78:600, 1944.

9. Kozoll and others.^{7o} Meyer and others.^{8f}

10. (a) Steigmann, F.; Meyer, K. A.; Kozoll, D. D.; Volk, B. W., and Popper, H.: Gelatin Solution in Plasma Substitutes, to be published. (b) Kozoll and others (footnotes 7o and 8c). (c) Meyer and others.^{8f}

11. Kozoll and others.^{7o} Meyer and others.^{8f}

12. Wintrobe, M. M.: *Clinical Hematology*, Philadelphia, Lea & Febiger, 1942.

and after administration of the hydrophilic colloid, was used for purposes of comparison. The other clinical and laboratory data obtained on these patients are not considered in this study.

From 4 patients who had received gelatin solution and from 3 who had received pectin solution, biopsy specimens of the liver were obtained at various intervals after the infusion on the occasion of a laparotomy, which was indicated by the underlying disease. Autopsy material was obtained from 12 patients who had received various doses of gelatin solution and from 10 who had

TABLE 1.—Average Percentage Change of Hematocrit Value, Hemoglobin Concentration and Mean Corpuscular Hemoglobin Concentration

	Gelatin		Pectin	
	Hospital Controls	Patients in Shock	Hospital Controls	Patients in Shock
Number of cases.....	75	77	61	73
Average percentage decrease of hematocrit value after administration of:				
1,000 cc.....	11.6	19.5	10.3	18.8
2,000 cc.....	17.1	15.9
3,000 cc.....	19.3	16.1
Average percentage decrease of hemoglobin concentration after administration of:				
1,000 cc.....	8.5	16.4	6.7	14.7
2,000 cc.....	12.6	12.8
3,000 cc.....	18.8	14.8
Average percentage increase of mean corpuscular hemoglobin concentration after administration of:				
1,000 cc.....	0.31	0.88	1.0	1.8
2,000 cc.....	2.0	1.2
3,000 cc.....	0.1	2.8

received pectin solution at different intervals before their death.

The gelatin (with an average molecular weight of approximately 35,000) was provided by the Upjohn Company (Kalamazoo, Mich.) in 5 per cent solutions; one solution consisted of 5 per cent gelatin in isotonic solution of sodium chloride, another of 5 per cent gelatin in 5 per cent dextrose solution and another of 5 per cent gelatin fortified with tryptophan, tyrosine, methionine and cystine. The gelatin was prepared from bone collagen by a process of electrodialysis. The calcium gelatinate was then autoclaved, mixed with distilled water, sodium hydroxide, phenylmercuric borate and sodium chloride, passed through a sterilizing filter and autoclaved again. The pH of the end product was of physiologic range, with a viscosity of 2 centipoises and an oncotic pressure of 70 mm. of mercury (± 5 mm.). The pectin solutions were prepared by Frederick Stearns & Company (Detroit) in 0.9 per cent sodium chloride; the molecular weight was around 55,000. The viscosity varied between 3.55 and 4.68 centipoises; the pH ranged between 3.91 and 3.70. The original pectin, which is obtained from citrus fruit, is a carbohydrate-like substance composed of a long-chained molecule consisting chiefly of polymerized galacturonic acid molecules with the addition of various smaller groups. Its molecular weight varies between 45,000 and 60,000 and is reduced from 250,000 by autoclaving in the process of preparing the solution. Hueper^{5a} emphasized the difference in the reactions elicited in the tissues by pectin solutions of different molecular weights. The pectin solutions were adjusted by phosphate buffers to a pH of about 7.2 before intravenous administration.

OBSERVATIONS ON HUMAN BEING

I. Hemodilution.—Gelatin and pectin were equally efficient in producing dilution, as indicated by the percentage of hemoglobin concentration or hematocrit after the administration of comparable (table 1). Both substances produced more hemodilution in patients in shock than in control subjects. There was a difference in the degree of hemodilution as determined by hemoglobin concentration or the hematocrit value; the hematocrit level dropped more in instances than the hemoglobin concentration. Consequently, the mean corpuscular hemoglobin concentration increased equally with each after its administration both to patients in shock and to those not in shock. The increase appears for mathematical reasons less than the mean of the individual concentrations taken than if it is calculated from the average of the hematocrit values and hemoglobin concentrations.

Administration of additional gelatin or solution over the initial 1,000 cc. produced less hemodilution in all the instances recorded.

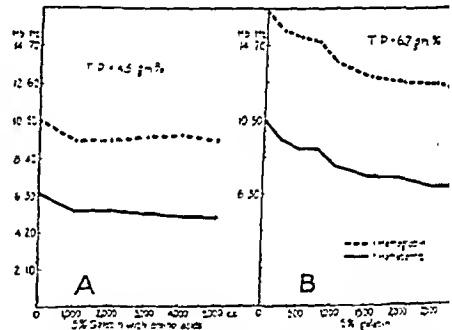


Fig. 1.—Serial determinations of the hematocrit and hemoglobin values following continuous infusion of gelatin solution to a hypoproteinemic patient (A) and a person with acute alcoholism (B). The inability to produce significant hemodilution in patient A, whose protein and hemoglobin reserves were depleted, is apparent. Patient B, whose protein and hemoglobin values were normal, shows progressive hemodilution which tends to decrease with increasing amount of fluid. The total protein content for patient A is 4.5 and for patient B 6.7 Gm. per hundred cubic centime

Consistently with both substances the hemodilution curve leveled off. The leveling off was uniform, in contrast to the initial percent change of hemoglobin concentration and hematocrit value, which was similar in all cases observed. In an attempt to establish the factor responsible for these variations of the hemodilution curve after administration of larger amounts we found that for patients with anemia or hypoproteinemia the hemodilution curve leveled off

ich earlier than for patients with a normal blood count and adequate protein reserves (fig. 1).

II. Sedimentation Rate of Erythrocytes.—The sedimentation rates of almost all patients rose after the administration of gelatin or pectin solution (table 2). The rise was of about equal degree for the two groups. The sedimentation rates of patients in shock increased more than those of hospital control subjects, because the initial sedimentation rates of the patients in shock were lower, which permitted a higher rise. Again,

TABLE 2.—Influence of Intravenous Administration of Gelatin and Pectin Solutions on the Sedimentation Rate of Erythrocytes

	Gelatin		Pectin	
	Hospital Controls	Patients in Shock	Hospital Controls	Patients in Shock
Number of cases.....	75	77	61	73
Average increase of the sedimentation rate in mm. per hr. after administration of:				
1,000 cc.....	15.1	23.8	12.6	24.3
2,000 cc.....	17.9	20.0
3,000 cc.....	20.3	18.6

TABLE 3.—Results of Histologic Examination of Organs of Patients Who Had Received Various Amounts of Gelatin

Age	Race	Sex	Clinical Diagnosis	Amount Injected, Cc.	Number of Injections	Interval Between First Injection and Examination	Liver	Spleen	Kidney
45	W	M	Carcinoma of the bladder.....	6,000	2	3 days	—	—	vvv*
70	W	M	Icteric cirrhosis; ascites.....	4,200	2	60 hours	—	—	vv
55	W	M	Carcinoma of prostate.....	3,000	1	12 hours	—	—	vv
33	W	F	Carcinoma of cervix uteri.....	2,300	2	4 hours	—	—	—
21	W	F	Thrombosis of splenic vein; hypoproteinemia	9,000	7	26 days	—	—	—
60	W	M	Carcinoma of stomach.....	3,000	3	65 days	—	—	—
44	W	F	Carcinoma of cervix uteri.....	4,000	3	18 days	—	—	—
63	W	M	Carcinoma of stomach.....	5,000	3	9 days	—	—	dt
50	W	M	Bacterial endocarditis	3,000	2	4 days	—	—	—
45	W	M	Toxic hepatitis	1,200	1	12 hours	—	—	—
68	W	F	Coronary occlusion	1,000	1	12 hours	—	—	—
37	W	F	Carcinoma of cervix uteri.....	1,200	1	10 hours	—	—	—
45	W	M	Carcinoma of stomach.....	1,000	1	8 hours	—	—	Biopsy
48	W	F	Obstructive jaundice	1,000	1	6 hours	—	—	Biopsy
51	W	F	Pyloric obstruction	2,000	2	2 days	—	—	Biopsy
36	W	M	Bleeding peptic ulcer.....	2,000	2	6 days	—	—	Biopsy

* v indicates vacuolation of the tubular epithelial cells.

† d indicates dilatation of the glomerular spaces and tubules.

TABLE 4.—Results of Histologic Examination of Organs of Patients Who Had Received Various Amounts of Pectin

Age	Race	Sex	Clinical Diagnosis	Amount Injected, Cc.	Number of Injections	Interval Between First and Last Injection	Interval Between Last Injection and Examination	Liver	Spleen	Kidney
30	N	F	Intestinal obstruction	2,000	1	8 hours	—	—	ddd †
65	N	F	Carcinoma of colon	2,000	2	1 day	12 hours	—	—	d
43	W	M	Nephrosis; hypoproteinemia	9,000	9	19 days	3 days	vvv* †	pppp e;	pppp
15	N	M	Nephrosis; hypoproteinemia	7,000	14	15 days	26 days	vv pp	pppp eee	pppp
72	W	M	Decubital ulcers; sepsis.....	4,300	5	14 days	18 days	—	ggg ‡	—
73	W	M	Injury to spinal cord; paraplegia.....	6,000	3	6 days	20 days	—	eeee ppp	—
49	W	M	Carcinoma of stomach.....	6,000	3	3 days	2 days	—	gg e	p
55	W	M	Intestinal obstruction	4,000	2	1 day	12 days	—	—	—
48	W	F	Peritonitis	2,000	2	2 days	—	—	—
79	N	M	Carcinoma of stomach.....	2,000	2	1 day	1 day	—	—	—
21	N	M	Sickle cell anemia; hepatitis.....	1,000	1	1 day	—	—	Biopsy
55	W	F	Carcinoma of stomach.....	2,000	2	1 day	—	—	Biopsy
40	W	M	Bleeding peptic ulcer.....	1,000	1	1 day	—	—	Biopsy

* v indicates vacuolation.

† p indicates deposition of a material staining with ruthenium red.

‡ e indicates endothelial cell proliferation.

§ g indicates giant cells.

¶ d indicates diuresis.

rise of the sedimentation rate did not continue with additional administration of gelatin and pectin solutions, and the third liter of both substances had almost no effect.

III. Changes in the Tissues in Human Beings.

—A. Gelatin: A morphologic change possibly attributable to the administration of gelatin which was observed in the organs examined (liver, kidney, spleen, heart, lung and adrenal gland) was vacuolation of the epithelium of the

proximal and distal convoluted tubules of the kidney (table 3). The vacuoles were uniform and about half the size of a red cell. They crowded the epithelial cells, the nucleus being displaced to the base of the cells. The vacuoles failed to give a reaction for fat. They were not stained by Mallory's aniline blue stain or by ruthenium red. This change was observed in 3 patients who had received 6,000, 4,200 and 3,000 cc. of solution within the last one to three

days before their death. In the patient who had received 3,000 cc. in one infusion one day before death, a homogeneous material, which stained blue with hematoxylin and eosin, was seen in the greatly widened glomerular spaces and also in the dilated tubules of the kidney (fig. 2). In other patients, to whom smaller amounts were administered or for whom the interval between death and the last injection of gelatin solution was longer, this change was not observed. It should be stressed that a patient who had re-

lumens of the tubules belonging to the meruli were also greatly widened. This which simulates that seen in experimental animals during forced diuresis, was especially noticeable in 2 patients who had received cc. of pectin solution eight and twelve hours before death. In patients with a longer interval between the last injection of pectin solution and death these changes were not present.

2. Deposition of a peculiar material in with a cellular reaction. These deposits



Fig. 2.—Kidney of a patient who had received 3,000 cc. of gelatin solution twelve hours before death. The glomerular space and the tubular lumen are greatly dilated. The glomerular space is filled by blue-stained material. The epithelium of the convoluted tubules is extensively vacuolated.

ceived 2,300 cc. within the last thirty-six hours did not reveal this change, nor did another patient who had received 3,000 cc. three days before death.

B. Pectin: In the examined organs (heart, lung, spleen, liver, pancreas and kidney) of the patients who had received injections of pectin solution the following changes were encountered which could be attributed to the administration of pectin (table 4):

1. Dilatation of glomerular spaces and tubular lumens. The glomerular loops appeared to be immersed in the content of the widened glomerular spaces and compressed by it. The

observed in 4 patients who had received 4,300, 6,000, 7,000 and 9,000 cc. of the pectin solution with an interval of thirty-two, twenty-eight, forty-one and forty-nine days, respectively between the first administration and death.

1 patient, however, who had received 6,000 cc. with an interval of only five days between the first infusion of pectin solution and death, these changes were not observed. Altogether, in patients who had received less than 4,000 cc. of pectin solution or for whom not more than thirteen days had elapsed between the first infusion and death, no changes were encountered which possibly could be attributed to administration of pectin.

A characteristically stained structureless material was found in the pulp of the spleen (providing a variable degree of splenomegaly), in upper cells and portal triads of the liver, in omerular loops and in lumen of tubules of the dney and in capillaries and proliferated mononuclear cells of the lung. Histologically, the cture resembled amyloidosis. The material appeared purple in sections stained with hematoxylin and eosin, pink (different from the distinct red of the collagenous fibers) with Van Gieson stain and blue with Mallory's aniline blue stain. It did not give a reaction for amyloid, iron or calcium and it was not acid fast. In sections stained with ruthenium red,¹³ described as a specific stain for pectin,¹⁴ the material appeared selectively distinctly red. It was not digested if the method of Bjorkenheim¹⁵ was used. Smears of the pectin solution on glass slides were stained by ruthenium red but not by hematoxylin and eosin, Van Gieson stain or Mallory's aniline blue stain.

The deposition was accompanied by proliferation of reticulum cells and endothelial cells in the spleen, by proliferation of glomerular cells in the kidney with formation of giant cells and hyalinization of the loops and by mobilization of the Kupffer cells in the liver.

The changes varied greatly in the 4 patients, whose cases therefore are summarized:

REPORT OF CASES

CASE 1.—A 15 year old Negro youth gave a history of extensive pitting edema for over a week and occasional dizziness and dyspnea on slight exertion. The essential findings on admission to the hospital were edema, anemia, a blood pressure of 114 systolic and 84 diastolic and albuminuria; examination of the serum revealed a nonprotein nitrogen content of 54 mg. per hundred cubic centimeters and a total protein content of 3.7 Gm. per hundred cubic centimeters with an albumin-globulin ratio of 0.97; the value for cholesterol was 386 mg. per hundred cubic centimeters. He was given plasma and later pectin solution (7,000 cc. in fourteen infusions, the last twenty-six days before death) in an unsuccessful attempt to reduce the edema. Nine weeks after his admission to the hospital the blood

13. The following procedure was used: Deparaffined sections were stained for one minute with a freshly prepared 1 per cent aqueous solution of ruthenium red (Coleman & Bell Company, Norwood, Ohio), washed with distilled water, brought through alcohol and xylene and mounted in Canada balsam.

14. Mangin, M. L.: Sur les reactifs colorants des substances fondamentales de la membrane. *Compt. rend. Acad. d. sc.* **111**:120, 1890; Sur l'emploi du rouge de ruthenium en anatomie vegetale, *ibid.* **116**:653, 1893. Tobler, F.: Ueber die Brauchbarkeit von Mangins Rutheniumrot als Reagens für Pektinstoffe, *Ztschr. f. wissensch. Mikr.* **23**:182, 1906. Hueper.^{2a}

15. Oldenburg, R., quoted by Romeis, B.: *Taschenbuch der mikroskopischen Technik*, Berlin, R. Oldenburg, 1932.

pressure rose to 150 systolic and 105 diastolic. The spleen became greatly enlarged, and the patient died with symptoms of uremia. (A few days before death the serum nonprotein nitrogen content was 65 mg. per hundred cubic centimeters, with a total protein content of 2.7 Gm.). The pathologic diagnosis included acute glomerulonephritis with superimposed subacute glomerulonephritis, splenomegaly (1,005 Gm.) with a large infarct of the lower pole of the spleen, extreme generalized anasarca and pronounced dilatation of the left ventricle.

Histologic examination revealed in the pulp of the spleen large, irregularly outlined deposits of a material which stained purple with hematoxylin and eosin and red with ruthenium red. The deposition was diffuse, with only a few islands of pulp left intact. The staining of the material varied in intensity. In some places it appeared homogeneous and in others broken into smaller lumps; it even formed meshes in which isolated reticulum cells were embedded. The latter were irregularly proliferated and formed even multinuclear giant cells with much cytoplasm. Connected with the edge of the large deposits were irregularly interwoven fine strands of strongly colored material, which were arranged around apparently imbedded reticulum fibers. The sinuses appeared greatly dilated and usually contained mobilized cells only. In places, however, the material was found within the dilated sinus, surrounded by proliferated endothelial cells, which may form multinuclear giant cells and be mobilized from the wall. The giant cells were arranged in aggregates and contained in their cytoplasm or engulfed the material stained with ruthenium red. The lymph follicles were scarce and small (fig. 3A).

The glomeruli of the kidney were much smaller than normal. Their tufts were irregularly arranged and often matted together and adherent to the glomerular capsule. In places, proliferation of the glomerular cells and sclerosis of the loops were seen. Many loops were obstructed by thick, darkly stained plugs which gave a ruthenium red reaction. In those areas the entire wall of the loop was thickened and gave a lighter ruthenium red reaction. The glomerular cells were scarce. Some of these infiltrated loops were adherent to each other and to the capsule. These foci were surrounded by proliferated glomerular cells and sclerotic connective tissue fibers, appeared dark blue with hematoxylin and eosin and gave a pronounced ruthenium red reaction but revealed also calcification with Von Kossa's stain. Some material stained with ruthenium red was found in the glomerular space; also in the often dilated tubules concentrated casts with a distinct ruthenium red reaction were encountered. Extensive proliferation of the intertubular connective tissue, occasionally with cellular infiltration, was noted throughout and was due to subacute nephritis (fig. 3B).

The hepatic cell cords showed a normal appearance. Some of the Kupffer cells were irregularly shaped, sometimes appearing as giant cells, and were mobilized from the hepatic cell cords. Their cytoplasm contained one or more droplets which stained with ruthenium red. Occasionally in enlarged portal triads capillaries were obstructed by plugs of ruthenium red-staining material; the same material was deposited in proliferated connective tissue fibers.

Also, in the lung some dilated capillaries in the alveolar septums contained plugs that stained with ruthenium red. Around them multinucleated giant cells were found which contained ruthenium red-staining material.

CASE 2.—A 43 year old white man had been treated for glomerulonephritis for the past two years. He was admitted to the hospital with puffing edema of the face and extremities. The blood pressure was 130 systolic and 90 diastolic. His urine contained much albumin and some red cells and lipid casts. The serum showed a nonprotein nitrogen content of 62 mg. and a creatinine

content to 5.6 mg. per hundred cubic centimeters; the total protein content fell to 2.6 Gm. per 100 centimeters, with an albumin-globulin ratio of 1 to 1. The patient died with uremic symptoms. At autopsy glomerulonephritis with nephrotic syndrome, general anasarca and passive congestion were noted. The spleen weighed 235 Gm.

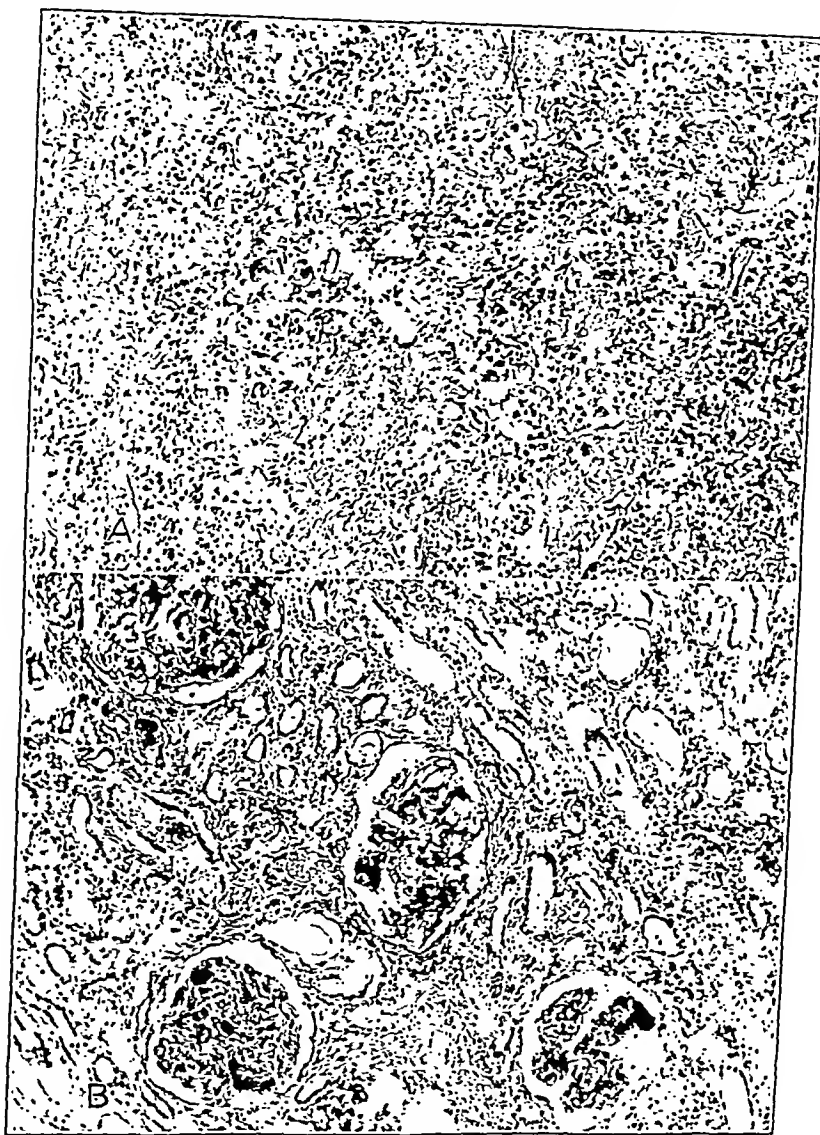


Fig. 3.—A, spleen in case 1. Large, irregularly outlined deposits of ruthenium red-stained material are in the pulp of the spleen. The sinuses are dilated and contain in places the same material surrounded by multinuclear giant cells. B, kidney in case 1. The loops of the glomeruli are obstructed by darkly stained material which give a strong reaction with ruthenium red. The wall of the loops has imbibed similar material, and appreciable sclerosis and calcification are present.

content of 5.2 mg. per hundred cubic centimeters; the total protein content was 3.8 Gm. per hundred cubic centimeters, with an albumin-globulin ratio of 0.9. In a frustrated attempt to correct the edema, he was given within forty-six days 9,000 cc. of pectin solution in nine individual infusions, the last one three days before death. The nonprotein nitrogen content (determined a few days before death) rose to 87 mg. and the creatinine

Histologically, in the pulp of the spleen the characteristic material was diffusely deposited in the form of a dense interlacing network with threads of variable thickness. Some of them were wide, homogeneous and less deeply colored, and others were thin and deeply colored; they were apparently due to infiltration of reticulum fibers. No reaction of the cells of the pulp was noted. The scarce sinuses were free of the material.

revealed extensive proliferation of the endothelial cells. The lymph follicles contained only a small center of lymphoid elements, which was traversed by fibers giving a reaction with ruthenium red. This center was rounded by a hemorrhagic zone, which was followed by an area with diffuse deposition of material stained with ruthenium red, in which, however, the shadows of the follicular structure were still apparent. The larger

plugs. Only a few nuclei were usually seen around the swollen walls of those loops in which a basement membrane could not be made out. The loops were often matted together and surrounded by cellular reaction (fig. 4A). In places multinuclear giant cells, apparently derived from glomerular cells, were seen on the surface of the swollen loops. Ruthenium red-stained material was scarce in the capsular space. Some

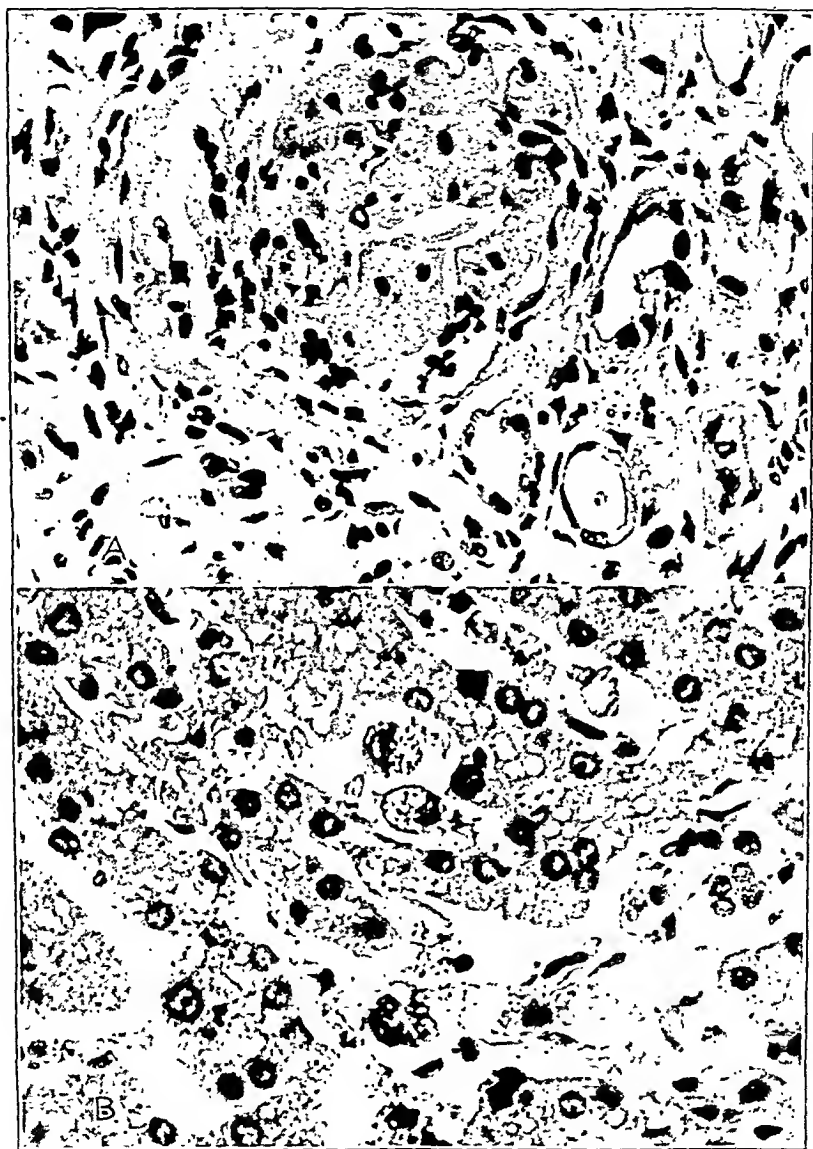


Fig. 4.—A, kidney in case 2 (high power). There are noticeable widening of glomerular loops, due to uniform imbibition with ruthenium red-stained material, and cellular reaction around the loops. B, liver in case 2 (high power). There is vacuolation of the cytoplasm of mobilized large Kupfer cells lying in the sinuses. The vacuoles give a reaction with ruthenium red.

vessels and trabeculae were almost entirely surrounded by the characteristic material.

The glomeruli of the kidney were usually enlarged. In the lumens of the loops in places plugs densely stained with ruthenium red were seen. The walls of the loops appeared as a whole greatly thickened and homogeneous but gave a less strong reaction to ruthenium red and also to Mallory's aniline blue than the

glomeruli underwent sclerosis, and here some fibers appeared soaked with the characteristic material. In the tubules concentrated casts with a strong ruthenium red reaction were noted. The intertubular connective tissue was increased and revealed lymphatic infiltration.

The liver showed small central areas of necrosis. In the intact areas the hepatic cell cords revealed many vacuoles which did not give a ruthenium red reaction.

The Kupffer cells, however, were often considerably enlarged and bizarre in shape. Their abundant cytoplasm contained several droplets which were stained by ruthenium red (fig. 4 B). Occasionally imbibition of connective tissue fibers with the characteristic material was noted in the portal triads.

CASE 3.—A 72 year old white man was admitted to the hospital with senile arteriosclerosis, dementia,

Histologically, the picture of the spleen was noted by proliferation of endothelial and even in reticulum cells with formation of large multinucleated cells of the character of foreign body giant cells. Pulp cords were often almost completely replaced by the proliferated reticulum cells. Many sinuses were free, while others were dilated and filled entirely by the irregular endothelial cells (fig. 5 A). Between the

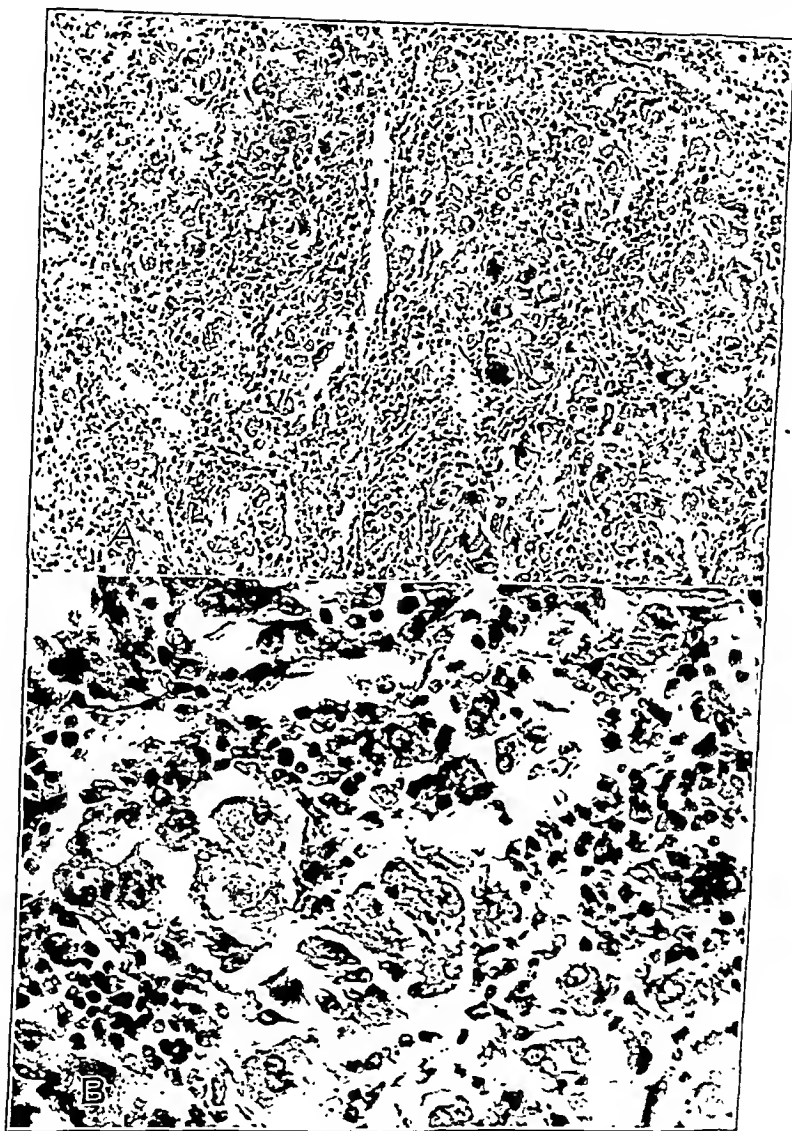


Fig. 5.—A, spleen in case 3 (low power). Extensive proliferation of the reticulum and endothelial cells with formation of giant cells obscures the normal architecture. B, spleen in case 3 (high power). Proliferation of reticulum cells with formation of giant cells surrounds shredded ruthenium red-stained material. A sinus is free.

debility, a large decubital ulcer over the sacrum and extensive furunculosis. As an adjunct to fluid therapy, the patient received 4,300 cc. of pectin solution in five injections. He succumbed with symptoms of bronchopneumonia.

At autopsy bronchopneumonia of the lower lobe of the left lung, hemorrhagic cystitis and moderate dilatation of both ventricles of the heart with passive congestion were found. The spleen weighed 230 Gm.

liferated reticulum cells and occasionally between the endothelial cells small amounts of material stained with ruthenium red were seen, mostly in shredded form. The cells engulfed and sometimes included it (fig. 5 B). Only small areas of intact pulp were seen. The lymph follicles were small and compressed.

The glomeruli of the kidney were only slightly enlarged, and some showed in places proliferation of cells; others were sclerotic. In some of the loops were plugs

ly stained with ruthenium red, around which formation of giant cells was noted. Similar material was found in Bowman's spaces and in the form of casts in glomeruli. The interstitial tissue revealed focal infiltration by lymphocytes and plasma cells.

In the liver, which revealed small foci of necrosis and congestion of the portal triads, some Kupffer cells contained droplets stained with ruthenium red.

CASE 4.—A 73 year old white man gave a history of fracture of the spine fifty years ago with subsequent paraplegia and paralysis of both lower extremities. He was afflicted with large decubital ulcers over the sacrum and died with signs of septicemia. Among other fluids 100 cc. of pectin solution was given in three infusions. The essential changes noted at autopsy were: dilation of the left ventricle of the heart with brown

CHANGES IN THE TISSUES IN EXPERIMENTAL ANIMALS

Five rabbits which had received 230 to 480 cc. of gelatin solution over a period from twelve to thirty-eight days and which were killed shortly afterward showed no changes in the tissues attributable to administration of gelatin except for some proliferation of Kupffer cells in the liver and alveolar cells in the lung in the rabbit which had received the largest amount.

Of 5 rabbits which had received 295 to 865 cc. of pectin solution within twelve to eighty-six days, 1 showed marked splenomegaly. All of

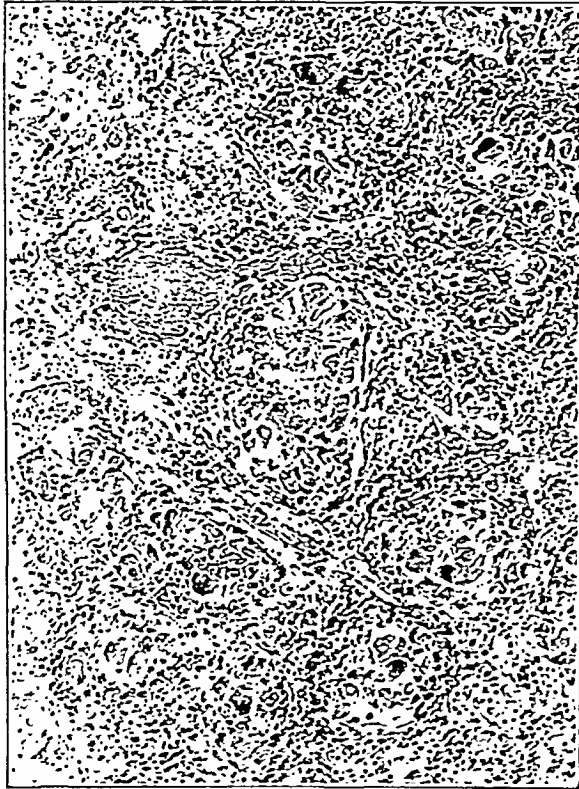


Fig. 6.—Spleen in case 4. Foci of proliferated reticulum cells with formation of giant cells engulf some ruthenium red-stained material.

atrophy, chronic passive congestion, arteriosclerosis of the aorta and coronary arteries and old compression fracture of the eleventh and twelfth dorsal and first lumbar vertebra. The spleen weighed 225 Gm.

Histologically the structure of the pulp and the follicles in the spleen was in general preserved. Only in small scattered foci a proliferation of reticulum and also of endothelial cells was noted, with formation of foreign body giant cells. Small amounts of irregularly formed ruthenium red-stained material were surrounded by the proliferated cells, which were seen in the pulp and only rarely filled a dilated sinus (fig. 6).

In tubules of the kidney ruthenium red-stained casts were seen; otherwise, no changes attributable to the administration of pectin were encountered in the kidney or the liver.

them revealed alterations of various intensity which were similar to those observed in cases 1 and 2. The changes found in the spleen and kidneys and the amount of material stained with ruthenium red far exceeded those found in human beings.

COMMENT

The gelatin and pectin solutions used produced a comparable hemodilution (which probably means increase in blood volume) as far as degree, duration and relative leveling off of the hemodilution curve with use of larger doses are concerned. The results of quantitative com-

parison agree with the impression gained from clinical observations of patients in shock. This deserves emphasis because the gelatin and the pectin solution used differed greatly in chemical nature, in concentration and even in physical characteristics. The condition of the patient, namely the presence of shock, influences the results more than the nature of the macromolecular solution. Of the first 1,000 cc. of both solutions, a certain percentage, about equal in the two instances, remains in the circulation, whereas of the additional doses a much smaller, again about equal, percentage stays in the blood stream. This partial exhaustion of the process of hemodilution is possibly due to an escape of the macromolecular substance from the circulation after it has reached a threshold. Investigations by others on gelatin¹⁶ and by our group¹⁷ on pectin have revealed that both substances are excreted in the urine relatively soon after administration and, furthermore, that the plasma level is decreased greatly at a time when the hemodilution is still maintained. These findings could be explained by the assumption that the macromolecular substance, which starts the hemodilution, leaves the circulation and is substituted by something else which maintains it, at least partly. The labile plasma proteins which potentially enter the circulation are possibly responsible for this mechanism.¹⁸ This would agree with the presented experiences in which hemodilution following the administration of large doses was less severe in patients with anemia or hypoproteinemia, for whom an exhaustion of the labile protein depots could be assumed. If this concept is right, the presence of the macromolecular substance, independent of its nature, elicits a response which could be called an autotransfusion with plasma proteins and which is possibly part of the hematologic reaction of Hueper.³

The increase in the sedimentation rate, which is an index of the pseudoagglutination of the red cells and which was selected as an example of the hematologic changes, is of the same degree in both instances and again levels off with the administration of higher doses. Whether the increase of the sedimentation rate is of practical significance is sub judice; however, there is no difference between the sedimentation rate following administration of gelatin and that following administration of pectin.

The two substances differ decisively, in the production of changes in the Gelatin causes only a transient vacuolation of proximal convoluted tubules in the Chemical identification of these droplets is possible; however, one can assume that they were due to reabsorbed gelatin which water and caused the hydropic swelling morphologically simulates that produced by sucrose.¹⁹

The dilatation of the renal tubules and interglomerular spaces after administration of pectin as a transient sign of forced diuresis, is insignificant; not so, however, is the deposition of a peculiar material in spleen, liver and lung, which somewhat resembles amyloidosis. In the spleen the material is enlarged after administration of pectin, much of the material is deposited in the spleen. The deposition is in the capillaries, where it may be concentrated as in the glomeruli, where blood is concentrated or in the lung. It may penetrate into the interstitial spaces and may fill them completely, as in the pulp of the spleen or the portal triads of the liver. It often appears concentrated in the interstitial spaces, and the impression is gained that it is precipitated around reticulum fibers and infiltrates. It is also taken up by Kupfer cells of the liver, reticuloendothelial cells of the glomerular cells of the kidney and alveolar cells of the lung. The material is an irritant and causes severe reaction of the reticuloendothelial cells and hyalinization of renal glomeruli.

The nature of the material is not established. The selective staining with ruthenium red suggests pectin. However, the specificity of the ruthenium red reaction in tissues deserves further investigation. It is possibly a polymerization product of pectin with a higher molecular weight than that of the injected pectin.²⁰ The staining with dyes which do not stain pectin suggests an admixture of other substances, possibly of protein nature.

Whatever the nature of the material, it is related to retention of pectin in the tissues, so since similar pictures were produced by administration of pectin to animals by Hueper and ourselves. The difference between gelatin and gelatin is not surprising, since there is reason to suspect in tissue cells the presence of enzymes more capable of splitting gelatin than pectin.

16. Parkins and others.¹⁶ Little and Dameron.¹⁶

17. Kozoll, D. D.; Volk, B. W.; Stiegmann, F., and Popper, H.: Pectin Excretion in Humans, to be published.

18. Taylor and Moorhouse.¹⁸ Parkins and others.¹⁷

19. Anderson, W. A. D., and Betha, W. R.: Renal Lesions Following Administration of Hypertonic Solutions of Sucrose: Report of Six Cases, *J. A. M. A.* 114:1933 (May 18) 1940.

How significant is the deposition of pectin organs? The histologic picture does not include the possibility that the uremia in the 2 patients with nephrosis who had received pectin solution was due to the deposition of the peculiar material in the glomeruli. However, the amounts of pectin solution which produced the reported changes are far in excess of those given to patients in shock. We do not know whether other pectin solutions, which are subjected to prolonged autoclaving and are of smaller molecular weight, produce the same changes. Hartman²⁰ has informed us that in similar studies on human beings and animals the pectin solutions failed to produce changes comparable to ours. He stated that our pectin solutions were prepared by a method subsequently modified by him. We are aware that the physicochemical nature of a given macromolecular solution is of great significance. In addition, it should be stressed that with quantities ordinarily used in the treatment of shock such changes in the tissues have not been observed.

As regards the solutions used by us, despite equal physiologic and therapeutic efficiency, gelatin deserves preference over pectin as a substitute for plasma in the treatment of shock in view of possible changes in the tissues. If the need for a substitute for plasma of nonhuman origin should arise for an autotransfusion of plasma proteins, gelatin should first be considered because of less tissue reaction.

20. Hartman, F. W.: Personal communication to the authors.

SUMMARY

Experiences with administration of gelatin and pectin solutions—which were used as substitutes for plasma in the treatment of shock—to a series of 317 patients in shock and not in shock were compared. The two solutions produce an equal degree of hemodilution which levels off with administration of higher doses of both solutions. This leveling off is more pronounced in patients with anemia and hypoproteinemia. The hypothesis is suggested that the hemodilution is started by the macromolecular solution but maintained by other substances, possibly labile plasma proteins. Gelatin and pectin solutions produce an equal rise in the sedimentation rate, which is considered an index of hematologic changes. The significant difference between the two solutions lies in the fact that gelatin produces less change in the tissues whereas after administration of amounts of pectin in excess of those used for patients in shock splenomegaly and deposition of a peculiar material in various organs may be observed. The material is selectively stained by ruthenium red, a dye used for staining pectin. It is found in phagocytic cells, capillaries, tissue spaces and infiltrating reticulum fibers in the spleen, kidneys, liver and lungs; it resembles deposits of amyloid and causes a reaction of the reticuloendothelial cells. A similar picture was produced in animals by administration of large amounts of pectin. The clinical significance of these changes is admittedly unknown. Since the beneficial effects of gelatin and pectin appear equal on the basis of changes in the tissues, gelatin appears preferable to pectin in the form used.

MALIGNANT RENAL NEOPLASMS

A CLINICAL AND PATHOLOGIC STUDY

BENJAMIN S. ABESHOUSE, M.D., AND TOBIAS WEINBERG, M.D.
BALTIMORE

Aware of recent pessimistic expressions made by various authors concerning the prognosis for malignant renal neoplasms, we undertook this study in order to evaluate our diagnostic methods and also to determine the possible clinical and pathologic factors which influence the prognosis and are conducive to a higher survival rate. We have collated the data on 63 consecutive malignant renal neoplasms. Of the 63, 53 were confirmed by operation and 10 by necropsy. We have omitted data on all benign tumors of the parenchyma, pelvis and capsule.

PATHOLOGY

In reviewing the literature one finds numerous classifications of renal neoplasms, many of which are complicated and presented with lengthy arguments in their support. We have adopted a rather simple classification, which is presented in table 1, and which we feel combines the important histologic features with the anatomic site of origin of these neoplasms.

TABLE 1.—Classification of Sixty-Three Malignant Renal Neoplasms

	No. of Cases
I. Malignant tumors of the parenchyma	
A. Hypernephroma (Grawitz).....	48 (76.19%)
B. Adenocarcinoma	
1. Tubular.....	5 (7.94%)
2. Papillary.....	1 (1.58%)
C. Wilms tumor.....	3 (4.76%)
II. Malignant tumors of the mucosa of the pelvis or calices	
A. Transitional cell carcinoma	
1. Infiltrating.....	3 (4.76%)
2. Papillary.....	2 (3.19%)
B. Squamous cell carcinoma.....	1 (1.58%)
Total.....	63

Hypernephroma.—The most frequent type of malignant tumor observed in our series was the so-called hypernephroma. Because of the small number studied we do not feel justified in attempting to draw any far reaching conclusions as to the histogenesis of the malignant Grawitz

tumor. We are inclined to favor the view type of tumor is derived from nephrogen. In support of this theory we found th group of 48 hypernephromas 25 of th (52 per cent) were located in the n lower thirds of the kidney. However, unable to find deposition of hyaline dr the large polyhedral cells which line the lumens, as has been described by some pri of this theory.¹

The hypernephromas in our series wer or globular in shape, with an irregular or surface. The cut surface possessed a ric color with interspersed areas of heme necrosis and fibrosis. Small deposits of salts within the tumor mass were frequ served. Although the tumor was usually marcatcd from the surrounding parench distinct fibrous capsule could not be demon in many cases. Many of the tumors show considerable variation in the cellular structur characteristic polyhedral clear or foam ce its small pyknotic nucleus predominate variations in the size, formation and arrang of the cells and their nuclei were frequently in the same tumor. In several cases tumor cells were seen. Mitoses were not infre accompaniments of these histologic vari. In several cases, cells with a granular cyto were found in isolated areas or in close prox to predominant groups of clear cells. I instance were granular cells the sole or prom cellular element. Consequently we did not a much significance to cytoplasmic changes differential diagnostic feature in dividing m nant Grawitz tumors into various histo types.

In the group of 48 malignant Grawitz tu there were 2 specimens in which malignant generation was observed in the walls of a soli cyst. Two neoplasms were found in conger anomalous kidneys, i. e., in the right half c horseshoe kidney and in the lower half c double left kidney.

From the Departments of Urology and Pathology, Sinai Hospital.

Read before the Section on Pathology and Physiology at the Ninety-Fourth Annual Session of the American Medical Association, Chicago, June 15, 1944.

1. Schiller, W.: Histogenesis of So-Called Grawitz Tumor, Arch. Path. 33:879 (June) 1942.

Adenocarcinoma.—We have restricted the use of the term adenocarcinoma to a relatively infrequent group of tumors which exhibit distinct tubular or papillary cellular arrangements. On cross examination these tumors show little or no features which distinguish them from malignant rawitz tumors, and they are not limited to any one portion of the kidney. Microscopic study showed considerable variation in the cellular structure. In several cases, the tumor was composed of fine strands of cells of a uniform low columnar nature, which were arranged in either tubular or papillary fashion. Mitotic figures were absent or rare. In 1 case, the tubules of the kidney were reproduced on a large scale and the individual cells were of unusually large size, arranged in concentric fashion with a central lumen and ensconced in a thin fibrous network. The cytoplasm was granular and in some instances vacuolated. An occasional cell was multinucleated.

Adenocarcinomas are apparently derived from the tubules of the kidney and probably represent adenomas which have undergone malignant changes.

It is noteworthy that the apparent gross encapsulation of the tumor mass in cases of hypernephroma and adenocarcinoma was found on microscopic examination to be distinctly incomplete. In many areas the tumor tissue appeared to be in direct contiguity with the compressed but intact renal parenchyma. In those cases in which a true tumor capsule did exist, it was composed of a dense but not very broad layer of connective tissue which was frequently invaded by tumor tissue.

Wilms Tumor.—The group of Wilms tumors was small (3 cases). All 3 cases came to necropsy at the Sinai Hospital. In 1 case, a woman aged 23 years had had the primary tumor of the left kidney removed elsewhere, where it was diagnosed as an embryonal carcinoma of the Wilms type. The histologic character of the locally recurrent tumor mass was readily discernible, as the patient had not received irradiation before or after operation. In the other 2 cases extensive irradiation before and after operation had been employed and had resulted in marked distortion of the microscopic picture.

The gross specimens of the 2 primary Wilms tumors which came under our direct observation were distinctly dissimilar. In 1 neoplasm was situated in the middle third of the kidney and on cross section presented a light brown bulging surface, which was fairly well demarcated from the surrounding parenchyma. The other specimen presented a most unusual appearance. Al-

though the tumor arose in the middle third of the kidney, it extended outward and upward along the medial surface, capping the upper pole of the kidney and forming a larger extrarenal than intrarenal mass. The cut surface of the tumor showed extensive hemorrhage and necrosis resulting from intensive irradiation.

Malignant Neoplasms of the Mucosa of the Pelvis and the Calices.—The relatively high incidence of the pelvic type of tumor, i. e. 6 cases (9.5 per cent), in our small series was striking. We encountered 5 neoplasms of the transitional cell variety (i. e. 3 infiltrating and 2 papillary) and 1 squamous cell carcinoma. The transitional cell carcinomas were fairly extensive growths which were not encapsulated and in the fresh state closely resembled grossly a Grawitz tumor; their true nature was revealed only on microscopic examination. Microscopically they showed a tendency to spread through the kidney in strandlike fashion with considerable fibrous reaction. In some areas they grew in broad sheets in a manner similar to that of Grawitz tumors. Strands of tumor cells were easily discernible within lymphatics and blood vessels. On the other hand, the 2 transitional cell carcinomas of the papillary type presented purely superficial growths, of which 1 extended down and involved the entire ureter and the other was localized to the lower half of the pelvis with projection into the upper third of the ureter. Associated with the latter growth was a distinct hydronephrotic process in the upper half of the kidney. In both transitional cell carcinomas the papillary folds were shallow and thin and microscopically closely resembled the fronds of vesicle tumors.

The single squamous cell carcinoma in our series was in a kidney which had had ligation of the pedicle some months before extirpation and when inspected was so distorted that any attempt to describe a picture which might be characteristic for a neoplasm of this cell type was nullified. Nevertheless, obliteration of a lower calix by a firm whitish tumor mass could be made out. Microscopically, the characteristic large polyhedral cells with intercellular bridges were evident and mitotic figures were numerous. The absence of true sarcoma of kidney in this small series is not unusual in view of the rarity of this tumor.

Metastases.—It is regrettable that the data concerning metastases are available for only 13 of the 48 malignant Grawitz tumors. In this small series the lungs were involved most frequently (7 cases). The bones and the liver were next (6 cases each). Other organs and structures involved were the regional lymph nodes (5), the

spleen (4), the adrenal glands (3), the opposite kidney (2), the heart (2), the brain (2) and the seminal vesicle (1). There was a local recurrence in the operative area in 2 cases. These data are in accord with the reports of other authors.

The series of neoplasms classified as adenocarcinoma, Wilms tumor and tumor of the pelvis were too small for statistical analysis. However, the most widespread distribution of metastases in our series occurred with squamous cell carcinoma of the renal pelvis.

ASSOCIATED PATHOLOGIC CONDITIONS

It is not uncommon for renal tumors to be accompanied by other lesions within the urinary tract or by disease involving other organs or systems. Associated lesions were present in 21 (33.3 per cent) of the 63 cases. The most common lesions were of the cardiac type, i. e. hypertensive heart disease (10 cases), arteriosclerotic heart disease (8 cases) and coronary heart disease (2 cases). Renal lesions were present in 14 cases, i. e. calculi in 5 cases, acute pyelonephritis in 2 cases and solitary cyst in 2 cases. Prostatic lesions were noted in 13 cases, i. e. benign hypertrophy (7 cases), median bar (4 cases) and calculi (2 cases). Lesions of the bladder were found in 3 cases, i. e. carcinoma in 2 cases and calculi in 1 case. Diabetes was present in 1 case and carcinoma of the large bowel in 1 case.

The relatively high incidence of renal calculi associated with renal tumors was rather impressive and in accord with the observations of other authors. Five malignant Grawitz tumors were associated with renal calculi (8 per cent). The preoperative symptoms of 3 were attributed to the calculi, and the tumors were diagnosed as operation. Two tumors were detected as solitary cysts on the basis of urographic findings and confirmed at operation; but when the cysts were opened at the operating table suspicious tumor tissue was found in the walls of the cysts, and the kidneys were removed.

One of the most striking observations in our study was the high incidence of multiple primary tumors. There were 5 of this type. Bilateral primary malignant Grawitz tumors were present in 1 case.

AGE INCIDENCE

Our findings are in accord with the reports of other authors. The hypernephromas were encountered most frequently in the sixth decade (30 cases) and in the seventh decade (12 cases). The oldest patient with a hypernephroma was 68 and the youngest 23. The 5 patients with

tubular adenocarcinoma were 51, 52, 55, 58 and 62 years of age respectively. The patient with the papillary adenocarcinoma was 25 years of age. The Wilms tumors were observed in 3 children, 3½ and 8 years old respectively, and 1 adult, aged 23. The oldest patient was 71 years of age and had a transitional cell carcinoma of the pelvis of the kidney.

SEX INCIDENCE

The neoplasms in our series involved 35 males and 28 females. The 48 Grawitz tumors occurred in 27 men and 21 women. There were 1 men and 3 women with tubular adenocarcinoma. The 1 papillary adenocarcinoma occurred in 1 woman. The 6 carcinomas of the renal pelvis occurred exclusively in males. The 3 Wilms tumors occurred in females. The 5 renal tumors observed in patients below the age of 25 years occurred in females.

KIDNEY INVOLVED

The various types of renal tumor exhibit a selective affinity for one kidney. In our series 31 neoplasms involved the right kidney and 31 the left; in 1 case there was bilateral involvement.

SYMPTOMS AND CLINICAL SIGNS

A careful study was made of the initial symptoms and their duration in order to determine their diagnostic and prognostic significance.

The most common initial symptom was hematuria, the next was pain and the least common a tumor mass. Hematuria was the chief complaint in 22 cases (35 per cent) and was combined with pain or mass or both in 11 additional cases (52 per cent). Pain was the initial symptom in 16 cases (25 per cent) and was accompanied by hematuria or a mass or both in 14 other cases (47 per cent). A palpable mass was the initial symptom in only 2 cases (3 per cent) but was associated with hematuria or pain or both in 9 cases (17 per cent).

We found that the duration of symptoms is extremely variable and that it is extremely difficult to estimate the average time which elapses between the appearance of the first symptoms and the institution of treatment. In 16 cases the symptoms were present for less than one month and in 30 cases symptoms were present from one to twelve months. We were surprised to note the high percentage of cases in which symptoms lasted from one to seven years and attribute this deplorable situation to negligence on the part of the patient or procrastination on the part of the physician.

Our experience has been that the nature and duration of the initial symptoms have little diagnostic or prognostic significance. However, the necessity for early recognition of and immediate attention to these early symptoms is obvious. It is unfortunate that frequently too great an interval elapses before the initial hematuria appears—the tumor becomes palpable and by this time the condition has advanced to an inoperable stage, precluding the possibility of a cure. On the other hand, the initial hematuria may serve merely as a warning of the presence of a serious but not hopeless condition.

Hematuria.—Hematuria was the most striking symptom in our series. It was observed in 51 cases (81 per cent), being macroscopic in 38 cases (60 per cent), microscopic in 13 cases (21 per cent) and absent entirely in 12 cases (19 per cent). In 5 cases gross hematuria was a relatively late symptom, occurring weeks or months after the initial symptoms of pain or a mass. Not infrequently the hematuria was painless, lasted such a short time and occurred so long before the other symptoms presented themselves that both the patient and the physician disregarded its importance and were lulled into a false sense of security. In our experience the hematuria was rarely of sufficient intensity or amount to immediately endanger the life of the patient, although hematuria of such intensity has been reported. Hematuria must be regarded as an unfavorable prognostic sign, since its presence is dependent on invasion and ulceration of the mucosa of the pelvis or the calices by the neoplasm.

Pain.—Pain was the most frequent symptom in our series. It was present at some time or other during the course of the disease in 59 cases (94 per cent). The nature of the pain varied considerably. In a few cases, the pain was associated with hematuria and was due to the passage of long stringy clots, which occluded the ureter and caused distention of the pelvis. In most cases it occurred independently of hematuria or other symptoms and often preceded these symptoms by months or years. In such cases, the pain was spontaneous, intermittent or constant and was described by the patient as being of a dull "neuralgic" or "colicky" nature. The pain is usually localized to the lumbar region or to the overlying upper abdominal quadrants. In rare instances it may radiate along the distribution of the iliac, inguinal or genitocrural nerves and be referred to the lumbosacral joint, hips, thighs or knees. This occurred in 4 of our cases. In a few cases the pain was referred to the epigastrium

or lower abdominal quadrants and was attributed to displacement and pressure on adjacent organs by the tumor mass or to reflex irritation of these organs.

Tumor Mass.—A palpable tumor mass was noted in 40 cases (63.4 per cent) but was the chief complaint in only 2 cases (3.1 per cent). The frequency with which a tumor mass is detected is dependent to a considerable extent on the skill of the examining physician. Since renal tumors vary in size, shape, position and consistency, certain tumors cannot be palpated or can easily be overlooked.

Other Clinical Manifestations.—We were also impressed with the incidence of other clinical signs and symptoms associated with renal tumors.

1. Localized tenderness over the tumor, anteriorly or posteriorly, was present in 22 cases (34 per cent).

2. Loss of weight and strength was reported in 47 cases (74.4 per cent). Cachexia was observed as a late manifestation in 7 cases of advanced tumor (11 per cent), in which there were other outstanding symptoms of many months' duration.

3. Temperature varying between 101 and 103 F. and unaccompanied by evidence of infection in the urinary tract was present in 13 cases (21 per cent). The significance of hyperpyrexia in these cases is not clear, but it is presumably related to necrosis or hemorrhage within the tumor or to the liberation of toxic products by the tumor. In 3 additional cases the temperature was as high as 104.5 F., but this was accompanied by pyuria associated with pyonephrosis in 2 cases and with perinephritic abscess in 1 case.

4. Symptomatic varicocele (Guyon's sign) was observed in only 1 case (1.5 per cent); this occurred in a man aged 71 years who had a transitional cell carcinoma of the left renal pelvis and an adenocarcinoma of the sigmoid.

5. Urinary symptoms, i. e. urgency, frequency, nocturia, dysuria and burning, were reported in 16 cases (25 per cent) and were either associated with lesions of the prostate gland and bladder or accompanied by pyuria which was caused by infectious lesions of the kidney.

6. Gastrointestinal symptoms, i. e. nausea, vomiting, distention, eructation, vague abdominal pain and constipation, were observed in 11 cases (17.4 per cent).

7. Hypertension was observed in 11 cases (17.4 per cent). In 9 adults the preoperative blood pressure exceeded 160 systolic and 90 diastolic and after operation it dropped con-

siderably but soon rose to the preoperative or to a higher level in all but 2 of the patients. The blood pressure was 142 systolic and 84 diastolic in the 8 year old girl with a Wilms tumor and was not influenced by operation.

8. A slight or moderate degree of anemia was noted in the majority of cases, but a severe degree of anemia was present in only 9 cases (14.5 per cent).

The combined clinical triad of hematuria, pain and tumor mass was the chief symptom in 2 cases of advanced tumor and was noted in 21 cases during the course of the disease. These observations indicate the relatively infrequent occurrence and diagnostic unreliability of this combined triad in cases of renal tumor. In our experience the presence of this triad usually signified a far advanced and often hopeless condition.

In Wilms tumors in infants and in advanced or inoperable conditions in adults, the symptom triad may be reversed, i. e. a palpable mass and pain may exist for an indefinite period without hematuria.

Experience has shown that in order to establish early diagnosis it would be better to place less emphasis on this clinical triad and impress on the members of the medical profession and on the patients the serious import of blood in the urine, which should demand a thorough urologic study.

DIAGNOSTIC PROCEDURES

While the aforementioned signs and symptoms, as determined by a careful history and physical examination, have proved to be invaluable aids in the diagnosis of renal tumors, equally important is the information obtained by special urologic examinations, viz.: (1) urinalysis, (2) tests of renal function, (3) cystoscopy and (4) roentgenographic studies.

Examination of Urine.—A careful analysis of the urine should be done in every case of suspected renal tumor. The frequent occurrence of microscopic hematuria in our series is an indication of its diagnostic importance. The following urinary abnormalities were noted: microscopic hematuria (13 cases), gross pyuria (3 cases), microscopic red blood cells and pus cells (15 cases) and albuminuria (4 cases).

Tests of Renal Function.—We place greater reliance on phenolsulfonphthalein than on indigo carmine as a test of combined renal function. A phenolsulfonphthalein test and determination of the blood urea are done routinely on the patient's admission to the hospital.

Cystoscopic Study.—A complete cystoscopic examination is an indispensable aid in the diag-

nosis of renal tumors. The study should be formed with the patient under intravenous spinal anesthesia in order to allay his fear. One cannot emphasize too strongly to the patient and to the members of the medical profession the importance and necessity of performing cystoscopic study during the period of renal bleeding. The evil consequence of delaying examination until the hematuria has ceased enhances the diagnostic difficulties and militates against the possibility of a cure through an early diagnosis and operation.

Careful inspection of the bladder during the period of active bleeding enables the cystoscopist to determine the exact source of the bleeding, to rule out the presence of benign or malignant lesions of the posterior urethra, the prostatic vesical neck or the bladder.

A phenolsulfonphthalein test should be performed with each catheter in place. In some cases we found considerable diminution of function in the affected kidney, and in a few cases function was completely absent.

Roentgenographic Studies.—This procedure is one of the most valuable diagnostic methods at our disposal. A plain film should be taken shortly after the patient's admission to the hospital, at the time of cystoscopy, as it often discloses valuable information concerning alterations in size and shape of the kidneys as well as irregularities in the outline produced by renal tumors.

In the present study, retrograde pyelography was employed in 56 cases and intravenous urography in 10 cases. No urographic studies were performed in 7 cases, in which a renal tumor was not suspected but was disclosed at necropsy. In our clinic greater reliance is placed on retrograde pyelography than on intravenous urography. It is our contention that the diagnosis of renal tumor made on the basis of intravenous urographic findings is extremely difficult and hazardous in view of the frequent incomplete filling defects noted with this method, which are confusing and misleading. We prefer to use intravenous urography as a supplement and not a substitute for retrograde pyelography. Intravenous urography is useful for patients who are toxic or in the late stage of the disease, when cystoscopy and retrograde pyelography are contraindicated.

It is a routine procedure in our clinic to take stereoscopic films with a catheter in each ureter. This enables us to determine the degree of displacement of the ureter and the relation of the ureters to calcified shadows in and about the kidney. Before proceeding to take stereoscopic ureteropyelograms we make an accurate descrip-

ination of the renal pelvic capacity by distending the pelvis with measured amounts of sterile distilled water. This will indicate the amount of 20 per cent solution of skiodan sodium to be injected and at the same time give valuable information concerning the nature and location of the pain. We have employed lateral pyelograms in several cases in which the diagnosis was doubtful. When the diagnosis following retrograde pyelography is doubtful because of difficulty of excluding a filling defect or occlusion of the pelvis or calix due to insufficient injection of a pyelographic medium, it is advisable to repeat the pyelographic studies. In such cases we have intentionally over-distended the renal pelvis with 20 per cent solution of skiodan sodium and obtained a sharper delineation of the distorted, elongated or compressed calices and pelvis. We have also observed that with this method the contrast medium never penetrates the encapsulated hypernephroma but does penetrate the adjacent unaffected parenchyma by pyelotubular or pyeloparenchymatous back flow.

An analysis of the urographic findings in the 56 cases in which retrograde pyelography was employed are enumerated below:

	Cases
(a) Compression of one or more calices.....	53
(b) Elongation of one or more calices.....	51
(c) Partial or complete obliteration of one or more calices.....	48
(d) Dilatation of one or more calices.....	6
(e) Distortion or compression of the pelvis.....	26
(f) Dilatation of the pelvis.....	10
(g) Displacement of the pelvis.....	12
(h) Displacement of the ureter.....	15
(i) Calcification within the tumor.....	8
(j) Renal calculi.....	5

These pyelographic studies were of considerable value in establishing a correct preoperative diagnosis in 42 (75 per cent) of 56 cases in which retrograde pyelography was employed.

Experience has shown that comparatively little information relating to the particular histologic type of neoplasm is obtained from the changes just enumerated. As a rule, changes due to compression, distortion and occlusion in one or more calices accompanied by displacement of the pelvis or ureter occur more frequently with hypernephroma, whereas filling defects of the pelvis are more characteristic of carcinoma of the pelvis.

It is well to remember that there are many renal lesions which may produce one or more of these changes and must be considered in the differential diagnosis. These lesions include: (a) spasm of the pelvis, calices or ureter; (b) lesions within the pelvis or the calices, i. e. blood, pus, granulomas, cystic dilatations and air bubbles; (c) calculi in the pelvis or calices; (d) deformities associated with intrarenal obstructive or inflammatory processes, i. e. hydronephrosis,

pyelonephritis, pyonephrosis, cortical abscess and perinephritic abscess; (e) deformities associated with cystic disease, i. e. solitary cyst and polycystic disease; (f) deformities associated with extrarenal or retroperitoneal tumors; (g) deformities associated with congenital anomalies; (h) deformities associated with acquired ptosis or torsion.

Calcification within the tumor offered some diagnostic difficulty, as occasionally these areas of calcification were confused with renal calculi, calcification due to tuberculosis or calcification within a chronic pyonephrotic kidney. The singularity and the irregular patchy nature of these areas of calcification, which are usually found in necrotic areas near the center of the neoplasm, distinguish them from the multiple areas of fine granular calcification due to tuberculosis and from the sharp outline of renal calculi. The prognostic significance of calcification within renal tumors was also studied. It was found to have a favorable influence on 5 patients with hypernephromas; i. e. 3 patients lived sixteen, eleven and eight years respectively after operation and 2 were living and well four and five years respectively after operation. In 2 patients the calcification was associated with a transitional cell carcinoma of the renal pelvis, and these patients died one year and two months respectively following operation. Roentgenographic studies of the lungs and long bones should be employed routinely in every case of suspected renal tumor.

Diagnosis.—The preoperative diagnosis was correct in 41 cases (65 per cent) and incorrect in 18 cases (28.5 per cent); the condition was unsuspected but diagnosed at autopsy in 4 cases (6.5 per cent).

An analysis of the 18 cases in which an incorrect preoperative diagnosis was made is presented in table 2.

TABLE 2.—Analysis of Eighteen Cases in Which the Preoperative Diagnosis Was Incorrect

	No. of Cases	
(a) Renal calculus.....	2	(Stones found but tumor unsuspected)
(b) Calculous pyonephrosis.....	2	
(c) Pyonephrosis.....	3	
(d) Tuberculosis.....	3	
(e) Solitary cyst.....	2	(Cyst found but malignant changes in wall of cyst unsuspected)
(f) Perinephritic abscess.....	1	(Abscess found; tumor unsuspected)
(g) Chronic nephritis.....	1	
(h) Ovarian cyst.....	1	
(i) Splenomegaly.....	1	
(j) Retroperitoneal tumor.....	1	
(k) Acute empyema of gallbladder.....	1	
Total.....	18	

It is not always possible to distinguish the type of neoplasm present from clinical symptoms of

pain, hematuria and mass and urographic findings. One can, however, be guided by knowledge of the relative frequency and the age incidence of the various types of neoplasm.

TREATMENT

The only hope for the cure of renal neoplasms lies in early and complete removal of the affected kidney before metastases have developed. The feasibility of operative treatment requires the careful consideration of many factors, i. e. the condition of the patient, the nature and duration of symptoms, the size and mobility of the tumor and the presence of metastases. Each case presents a distinctly different problem, which may tax the skill and judgment of the urologist. Not infrequently seemingly hopeless patients are restored to apparent good health and economic usefulness after nephrectomy. Surgical treatment is also indicated in cases in which a doubtful or questionable diagnosis of renal tumor has been made, in order to determine the presence of a benign or a malignant lesion. An exploratory operation is indicated in every case of suspected renal neoplasm.

There is no unanimity concerning the advisability of operative treatment in the presence of metastases. It is generally agreed that surgical intervention is contraindicated in cases of multiple or disseminated metastases. There is some difference of opinion concerning surgical operation for patients with solitary asymptomatic metastasis in the lungs or the bones. In 1 of our cases, the right half of a horseshoe kidney containing a hypernephroma was removed because of severe bleeding and pain despite the presence of several isolated metastatic nodules in the lungs. The patient lived for eight months after operation.

There are two accepted avenues of approach for the removal of renal tumors, viz., lumbar and transperitoneal. It is generally agreed that the lumbar route is preferable for small or moderate-sized hypernephromas and for carcinomas of the pelvis. The lumbar route is also indicated when the diagnosis is uncertain. The transperitoneal approach is best suited for large and firmly fixed tumors, i. e. large Grawitz tumors, adenocarcinomas and Wilms tumors. The lumbar route also suffices in those cases in which irradiation has been employed preoperatively to shrink the tumor.

With the Wilms tumor, adenocarcinoma and squamous or transitional cell carcinoma of the pelvis, it is advisable to remove as much of the perinephritic adipose tissue as possible together with the kidney. For papillary carcinoma of the

renal pelvis, a complete nephroureterectomy including excision of a small segment of the wall, should be performed in one or two stages.

We wish to emphasize the importance of exposing the vascular pedicle as early as preferably before freeing or delivering the kidney. This enables the surgeon to expose the renal vein and the inferior vena cava and to remove them if present before the tumor permits ligation of the vascular pedicle, thus mobilizing the kidney. This precaution surely prevents the dislodging of tumor cells into the renal vein or the squeezing of tumor cells into the general circulation as a result of the forcible manipulation incident to the exposure and delivery of the kidney. In the present study tumor thrombi were deliberately removed from the renal vein in 1 case from the inferior vena cava before ligation of the pedicle. In all 3 cases the patient survived the operation for two years and failed to show evidence of metastases after the operation. Care must also be exercised to insure complete removal of the growth without rupturing the tumor. The escape of tumor cells into the perirenal tissue is usually responsible for a recurrence in the operative area or in distant sites.

The operability of a renal tumor should be based on the following features: (1) penetration of the tumor through its capsule; (2) presence of perirenal tumor infiltration; (3) absence of fixation of the tumor in the renal bed; (4) absence of secondary metastatic deposits in the perirenal and juxta-aortic lymph nodes and in intra-abdominal organs, and (5) presence of tumor thrombi in the renal vein and the inferior vena cava.

Röntgen Therapy.—Our personal experience with irradiation therapy has been extremely limited. Postoperative irradiation was employed in only 2 cases of hypernephroma, with no improvement or benefit. Preoperative and operative irradiation was employed in 2 cases of Wilms tumor in children. In the latter 2 cases the growth was extremely large and preoperative irradiation resulted in considerable reduction in the size of the growth and greatly facilitated removal of the tumor. Despite extensive preoperative irradiation, both children survived from regional extension and metastases two years after operation.

OPERATIVE MORTALITY

One of the most outstanding achievements of surgical treatment on the genitourinary tract

the past thirty-five years has been the great reduction in operative mortality following nephrectomy for renal tumors. This accomplishment is due partly to the refinements in surgical technique and improvements in anesthesia and partly to the more careful selection and preparation of patients for operation.

There has been a gradual reduction in the operative mortality from 30 (Garceau) to 50 per cent (Squier²) in the early period of renal surgery to 1.2 (Priestley³) to 2.8 per cent (O'Connor⁴).

Fifty-three of the neoplasms in our series were treated by nephrectomy, with 4 operative deaths (7.5 per cent). The operations included 6 transperitoneal nephrectomies, with no deaths, and 47 lumbar nephrectomies, with 4 deaths (8.5 per cent). The cause of death was shock in 3 cases, fourteen occurring twenty-four and forty-eight hours postoperatively respectively, and cardiac failure with hemiplegia in 1 case, occurring on the fourteenth postoperative day. An exploratory operation was performed in 5 cases, with 2 deaths (40 per cent); 1 death due to uremia and 1 due to cardiac failure occurred on the fourth postoperative day.

More than 50 per cent of the 53 nephrectomies were performed by the two attending urologists of the service (Dr. Goldstein—21; Dr. Abeshouse—12). The remaining 20 operations were performed by eleven members of the general surgical and gynecologic staffs.

SURVIVAL RATE

Despite the remarkable reduction in the operative mortality achieved in the past thirty-five years, the survival rate has not been appreciably increased in the same period. Consequently some writers have adopted a pessimistic attitude toward the value of operative treatment, particularly for parenchymal neoplasm and infiltrating type of carcinoma of the renal pelvis. The increasingly good results obtained following complete nephroureterectomy in cases of papillary carcinoma should help to overcome this defeatist attitude.

Of the 53 patients treated by nephrectomy, data concerning the length of life after operation were available on 44 of them; there were no available data on 5 of the patients, and there were 4 postoperative deaths.

2. Squier, J. B.: Boston M. & S. J. **161**:547, 1909.

3. Priestley, J. T.: Survival Following Removal of Malignant Renal Neoplasms, J. A. M. A. **113**:902 (Sept. 2) 1939.

4. O'Connor, V. J.: South. M. J. **34**:27, 1941.

Analysis of the data on survival for 34 of the patients with Grawitz tumors reveals:

	No. of Cases	Per Cent
I. Length of life following operation		
(a) Death within 1 year.....	5	14
(b) Death within 2 years.....	10	29
(c) Survival 3 years or more.....	11	32
(d) Survival 5 years or more.....	7	20
(e) Survival 10 years or more.....	5	14
(f) Survival 15 years or more.....	2	5
II. Living and well after operation		
(a) Living and well 4 years or more.....	15	23
(b) Living and well 5 years or more.....	5	14
(c) Living and well 10 years or more.....	2	5
III. Cures in terms of years		
(a) 3 year cures.....	11	32
(b) 5 year cures.....	12	35
(c) 10 year cures.....	7	20
(d) 15 year cures.....	2	5

Three patients with adenocarcinoma were alive and well one, three and five years respectively after operation. One patient with transitional cell carcinoma of the pelvis died within thirteen months, and 1 with squamous cell carcinoma died within two months. One patient with papillary carcinoma of the pelvis was alive and well five months after operation, and 1 died eighteen months after operation. All 3 patients with Wilms tumors were dead within two years.

PROGNOSIS

Much has been written concerning the various factors which influence the prognosis of renal tumors. These factors include: (1) nature and duration of symptoms, (2) general condition of the patient, (3) type, size and mobility of the tumor, (4) tumor thrombi in the renal vein, (5) metastases, (6) surgical treatment and (7) irradiation therapy.

The prognostic significance of the various clinical signs and symptoms has already been discussed. The general condition of the patient is an indication of the degree of malignancy. Slow-growing tumors which usually are of low grade malignancy have little effect on the general constitution. A rapidly growing tumor indicates a high grade of malignancy and may be accompanied by severe toxemia, anemia, loss of weight, fever and cachexia in a manner similar to that of a tumor of high grade malignancy elsewhere in the body.

Broders, Braasch and Griffin⁵ and their associates at the Mayo Clinic have repeatedly stressed the prognostic significance of the degree of cellular differentiation in cases of hypernephroma. They maintained that the length of life after operation was considerably longer in cases of tumor with lower grades of malignancy. They

5. Braasch, W. F., and Griffin, M.: Prognosis in Renal Carcinoma and Clinical and Pathologic Data Affecting It, J. A. M. A. **106**:1343 (April 18) 1936.

also maintained that the duration of preoperative symptoms was longer for tumors with lower grades of malignancy and that the duration diminished as the malignancy increased. Unfortunately too many pathologists have had inadequate experience or have failed to adopt Broders' gradation of malignant neoplasms, which is based on variation in morphologic characteristics, arrangement of cells and manner of growth. Consequently relatively few reports are available to substantiate the prognostic significance of cellular changes. Our personal experience with this method has not been satisfactory. We attempted to correlate the grading of tumors with the survival rate for our group of 48 Grawitz tumors. The majority of these tumors belonged to grades 1 and 2. Several were of grade 3, and only 1 belonged to grade 4 (Broders' classification). The duration of life was so extremely variable with tumors of the first three grades that we were unable to establish any definite relation between these factors or draw any definite conclusions.

The size or weight of the growth is no true indication of the degree of malignancy. It has been our and other authors' experience that small tumors may metastasize as quickly and extensively as larger ones. Generally speaking, the prognosis is better with small movable tumors than with large fixed tumors. The degree of fixation of the tumor is of greater prognostic significance than the size and weight. A firmly fixed tumor usually indicates perirenal adhesions or tumor infiltration, which seriously interferes with mobilization and delivery of the renal tumor and increases the likelihood of dissemination of tumor thrombi or cells. Involvement of the renal vein is not always a fatal sign but certainly decreases the chance of a cure.

The prognosis varies considerably with the different types of neoplasms. Hypernephromas appear to progress slowly at the onset up to a certain point, after which the virulence of the condition increases and the clinical course is rapidly downhill. In our experience the prognosis for hypernephromas was by no means entirely satisfactory, as a large percentage of the patients died within two years of operation, and death was usually caused by metastases and occasionally by local recurrence. The majority of recurrences were within two or three years after the operation.

Our experience with the other renal tumors has been too limited to warrant personal conclusions. However, a review of the literature reveals uniformly poor results for squamous and transitional cell carcinoma of the renal pelvis. The

outlook in cases of papillary carcinoma renal pelvis has improved considerably in the past few years, owing to the adoption of complete nephroureterectomy, which insures complete removal of the kidney, the ureter and a small portion of the adjacent vesical wall. The prognosis for Wilms tumor is far from satisfactory, and the use of preoperative and postoperative irradiation. Better results may be hoped for in the future, due to improvements and refinements in irradiation and operative technics.

CONCLUSIONS

A careful analytic study of 63 renal neoplasms observed in the past twenty years and a review of the literature warrant the following conclusions:

1. Renal neoplasms are more common in men than in women (5:4).
2. These neoplasms occur with equal frequency in each kidney.
3. Parenchymal renal neoplasms are observed most frequently in the sixth and seventh decades of life with the exception of Wilms tumors, which are observed in infancy and early childhood.
4. The most common initial symptom in our series was painless hematuria. Next in frequency were pain and a tumor mass.
5. The classic symptom triad, which may be observed at any time during the course of the disease, is found in the following order of frequency: (a) pain 94 per cent, (b) hematuria 87 per cent and (c) tumor mass 63 per cent.
6. This symptom triad is usually reversed in children with Wilms tumors and in inexperienced adults, in whom a mass is usually the present symptom.
7. Retrograde pyelographic studies were performed in 56 cases, and a correct preoperative diagnosis based on the pyelographic findings was made in 42 cases (75 per cent). In our clinic greater reliance is placed on retrograde pyelography than on intravenous urography in the diagnosis of renal neoplasms.
8. The most common urographic findings associated with malignant neoplasms in order of frequency are (a) compression of one or more calices, (b) elongation of one or more calices, (c) distortion or compression of the pelvis, (d) displacement of the ureter or the pelvis, (e) dilatation of the pelvis and (f) calcification within the tumor.

9. In parenchymal neoplasms the characteristic pyelographic change is compression, elongation

or obliteration of one or more calices. In vic tumors a filling defect of the pelvis is the most uncommon finding.

10. In our series of 53 neoplasms treated by nephrectomy, there were 4 deaths (7.5 per cent). These deaths occurred after lumbar nephrectomy. This low operative mortality compares favorably with that given in reports in the past forty years.

11. Surgical intervention is justifiable in every case of suspected renal neoplasm, despite the relatively low survival rate. Early diagnosis and operation increase the chance of cure.

12. The following factors influence the prognosis: (a) nature and duration of the symptoms, (b) condition of the patient, (c) type, size and

mobility of the tumor, (d) tumor thrombi in the renal vein and inferior vena cava, (e) metastases, (f) type of surgical treatment and (g) irradiation therapy.

13. The best results from the standpoint of survival following nephrectomy were obtained with Grawitz tumors, and the poorest results, following operative treatment for pelvic neoplasms.

14. Our results with Grawitz tumors were gratifying when considered from the standpoint of a three year cure (11 cases [32 per cent]), a five year cure (12 cases [35 per cent]), a ten year cure (7 cases [20 per cent]) and a fifteen year cure (2 cases [5 per cent]).

LIGATION OF THE FEMORAL VEIN FOR CHRONIC OCCLUSIVE ARTERIAL DISEASE

A REVIEW OF ONE HUNDRED AND EIGHTEEN LIGATIONS

S. THOMAS GLASSER, M.D.

NEW YORK

In 1941 Lesser and I¹ reviewed 20 cases in which ligation of the femoral vein was employed in the treatment of chronic occlusive arterial disease of the lower extremities. As suggested in our preliminary report, the encouraging results demanded further evaluation of this procedure. The present report includes 118 ligations of the femoral vein performed on 110 patients. The results are far from spectacular, but the value of this procedure as judged from our experience definitely places it in the armamentarium for the treatment of chronic occlusive arterial disease, along with the many fairly recent procedures that have appeared in the literature. When a chronic disease is confronted, great dependence is placed on palliative measures. Thus, one attempts to alleviate acute symptoms and also to prevent complications or further spread of the disease. Even when life expectancy is definitely short, palliation is attempted for humane reasons alone. These considerations are still further emphasized in the treatment of patients who in practically every instance are in the older age group and in addition have the increased hazards which accompany systemic degenerative lesions. For aged persons with arteriosclerosis with an incompetent peripheral arterial circulation one should employ any measure which may prevent the dreaded complication of gangrene and subsequent amputation, even though the outlook in view of other associated degenerative lesions greatly limits life expectancy. Ligation of the femoral vein would therefore be indicated when lesions on the foot such as ulcer or gangrene have not made their appearance but when arterial insufficiency is in evidence and the prognosis is obvious. Even in those cases in which gangrene is imminent, ligation of the femoral vein

has proved of definite value. Since morbid or mortality is not associated with this procedure and since it is easily and quickly performed with the area under local anesthesia, no objection can be offered to its use. Under the heading of "Surgical Procedures of Therapeutic Value" Herrmann² stated:

In most patients with obliterative disease of the arteries of the extremities, the real clinical problem is whether or not the development of the collateral arterial circulation can keep pace with the demands for blood which are being made as a result of the progressive vascular occlusion. From the therapeutic standpoint, therefore, two definite problems arise: first, what can be done to stimulate the development of a collateral arterial circulation; and secondly, what can be done to prevent bacteria from attacking the poorly nourished tissues of the extremity during the active and progressive stages of the disease.

The answers to these problems have brought forth a great many surgical palliative procedures, among which is included ligation of a major vein. All of these procedures actually attempt to bring about the ultimate development of collateral vessels, since this is the only means by which improvement can occur. As in other specialized fields of surgery, with proper indications and in selected cases, each procedure has its own merits. This series of ligations of the

2. Herrmann, L. G.: *Passive Vascular Exercises and Conservative Management of Obliterative Arterial Diseases of the Extremities*, Philadelphia, J. B. Lippincott Company, 1936, p. 142.

3. Achmatowicz, L.: *Resection of Femoral Artery and Vein as Method of Treatment of Gangrene of Lower Extremities Caused by Endarteritis Obliterans*, *Polska gaz. lek.* 13:424, 1934. Allen, E. V.: *Recent Advances in the Medical Treatment of Peripheral Vascular Diseases*, J. A. M. A. 113:2375 (Dec. 30) 1935. Brooks, B., and Johnson, G. S.: *Simultaneous Vein Ligation: Experimental and Clinical Study of Therapeutic Venous Occlusion*, *Ann. Surg.* 100:761, 1934. Fedorov, P. A.: *Treatment of Spontaneous Gangrene by Oppol's Petroff's Method: Binding Femoral Vein*, *Vestnik lek.* 16:177, 1929. Fraser, N. D.: *The Conservative Treatment of Thromboangiitis Obliterans: A Report of the Results of Ligation of the Femoral Vein in Six Cases*, *China M. J.* 45:519, 1931. Pemberton, J. de J., and McCaughan, J. M.: *Traumatic Lesions of Arteries: Indications for Therapeutic Ligations of Veins*, *Ann. Surg.* 96:1103, 1932.

From the Department of Surgery, New York Medical College, Flower and Fifth Avenue Hospitals and Metropolitan Hospital—Dr. Louis Rene Kaufman, director.

1. Glasser, S. T., and Lesser, A.: *Femoral Vein Ligation for Chronic Occlusive Arterial Disease*, *Am. J. Surg.* 52:100, 1941.

noral vein is, to the best of my knowledge, only large series reported in which this special procedure has been given sufficient clinical trial.

What physiologic principles are involved subsequent to ligation of the femoral vein? According to Macleod,⁴ the hydrostatic pressure of the capillaries is approximately 22 mm. of mercury. At the proximal (arteriolar) end the pressure is 32 mm. of mercury, while the distal (venular) portion has a pressure of 12 mm. However, in chronic occlusive arterial disease the capillary pressure is decreased to almost hydrostatic value. Starting at the heart, the force (pressure) of flow diminishes as the smaller vessels are approached, so that in the capillaries the flow is fairly constant under normal conditions, irrespective of the intermittent changes of pressure which correspond to the cardiac systole and diastole. It would be fair to assume that with an increase in venous pressure caused by ligation of a major vein the tension on the arterial side would increase sufficiently to open up collateral vessels and augment the vascular bed in general. This presupposes the presence of functioning and available collateral vessels for this purpose. In addition, ligation of the femoral vein reduces to some degree any element of vasospasm which may be present, since some interruption in the sympathetic pathway is incidental to the procedure.

Oppel⁵ in 1913 noted that in cases of arterial insufficiency elevation of the limb was associated with pallor and ischemic pain while dependency resulted in hyperemia and disappearance of pain. His explanation was, in effect, that in arterial occlusion when gangrene is impending the blood pressure is so low that with the leg in the horizontal position the hydrostatic pressure is sufficient to stop the circulation. In addition, since elevation of the leg normally decreases the femoral venous pressure to almost zero, it would be expected that where the arterial flow is poor this condition would be exaggerated. Furthermore, the decrease in venous pressure would result in a taking up by the veins of collateral arterial blood, which would further embarrass more distal regions of the limb. However, with the limb in the dependent position, the arteries dilate by virtue of the weight of the blood column, and the venous pressure increases.

4. Macleod, J. J. R.: *Physiology in Modern Medicine*, St. Louis, C. V. Mosby Company, 1938, p. 376-377.

5. Oppel, cited by Brooks, B.: *Surgical Applications of Therapeutic Venous Obstruction*, Arch. Surg. 19:1 (July) 1929.

Following this line of reasoning, Oppel⁶ favored ligation of the femoral vein. He stated: "Ligation of the vein is beneficial not because the outflow is reduced, but because reduction in the outflow favorably influences the arterial circulation." He predicted beneficial effects from ligation of the femoral vein for threatened senile gangrene, reasoning that an equalization between the arterial and the venous system of the extremity could be obtained by this method, whereby a slowed venous return allowed for better utilization by the arterial portion of the circulation. Oppel was the first to demonstrate experimentally that after ligation of a large artery ligation of its accompanying vein increased the pressure in the artery, and in 1913 he performed the first therapeutic ligation of the femoral vein. The large number of gunshot injuries to major blood vessels in World War I gave further impetus to interest in this procedure. The statistical work of Makins⁷ on experiences with gunshot wounds in the war made acceptable the principle of elective ligation of satellite veins at the time of ligation of a main artery, which caused a definite reduction in the incidence of gangrene of the extremities.

In an experimental study on rabbits, Brooks and Martin⁸ found that occlusion of the common and external iliac arteries was followed by gangrene in 15 of 21 animals; the same arterial ligation coupled with ligation of the common iliac vein caused gangrene in only 6 of 18 animals. In further experimental studies, Holman⁹ elaborated the principle that ligation of the femoral vein proximal to the site of arterial ligation caused an increase in intra-arterial pressure, which was greater than that obtained when ligation of the femoral vein was done at the level of or distal to the site of arterial occlusion. In 1927 Pearse¹⁰ offered the following experimental observations on cats to explain the lessened incidence of gangrene following ligation of both the artery and the vein: (a) ligation of the artery alone caused an immediate increase

6. Oppel, A.: *Ueber die gestaltliche Anpassung der Blutgefäße unter Berücksichtigung der funktionellen Transplantation*, Leipzig, H. Engelmann, 1910.

7. Makins, G. H.: *On Gunshot Injuries to the Blood Vessels, Founded on Experience Gained in France During the Great War*, Bristol, J. Wright & Sons, 1919, p. 251.

8. Brooks, B., and Martin, K. A.: *Simultaneous Ligation of Vein and Artery: An Experimental Study*, J. A. M. A. 80:1678 (June 9) 1923.

9. Holman, E.: *Surgery of Large Arteries with Report of Ligation of Innominate Artery, for Varicose Aneurism of Subclavian Vessels*, Ann. Surg. 85:173, 1927.

10. Pearse, H. E., Jr.: *A New Explanation of Improved Results Following Ligation of Both Artery and Vein*, Ann. Surg. 86:850, 1927.

of intra-arterial pressure; (b) ligation of both the artery and the vein caused still greater increase in the immediate arterial pressure; (c) the arterial pressures gradually returned to normal at the end of three weeks; (d) arteriograms taken at the end of three weeks showed a greatly increased arterial bed, greater when both the artery and the vein were ligated and when the venous ligation was done proximal to the site of arterial ligation (Holman's principle).

Theis,¹¹ in an early clinical trial of the method, expressed the opinion that concomitant ligation of the vein was valuable for only a temporary period in acute arterial obstruction and had no appreciable effect on chronic arterial diseases in which the gradual progress of the condition had given the collateral bed an opportunity to develop. Van Gorder¹² used ligation of the femoral vein in a small number of cases of thromboangiitis obliterans and obtained immediate relief of pain and cessation of spread of gangrene in 3 of 5 cases, with complete failure in 1 case. The benefits derived from ligation of the vein were attributed to the resulting increase in venous pressure, in residual arterial pressure and in the peripheral arterial circulatory bed. He stated the belief that periarterial sympathectomy performed at the time of ligation had no material effect on the result. At about the same time Brooke¹³ in England performed ligation of the femoral vein combined with periarterial sympathectomy for diabetic gangrene of the extremities. He was enthusiastic about the results obtained, noting improved pulsation of vessels, localization and demarcation of the gangrenous process, cessation of spread, relief of pain and an opportunity to amputate at a lower site when amputation became necessary.

Spurrell¹⁴ ligated the artery and vein in the extremities of cats and then made arteriograms to show the opening up of numerous fine collateral vessels, which were most distinct two to three weeks after ligation. In similar experiments conducted on frogs, he observed under direct visualization the immediate opening up

of numerous previously inactive small vessels.

Lewis and Grant¹⁵ and Collens and Wilensky¹⁶ stated the opinion that the effects of venous obstruction on the circulation are due to the hyperemia which on release of a venous obstruction. Writers give this as an argument against ligation of the femoral vein, even though decreases in pulse volume have been experimentally and clinically on the use of a cuff.

In discussing reactive hyperemia, Leriche¹⁸ noted that this can also be obtained by the apparatus of Collens and Wilensky which produces intermittent venous compression. Arteriosclerosis, a low hydrostatic pressure, nearly always present, a condition which can be corrected by venous hyperemia, while the filtration pressure so that fluids pass from the capillaries to the tissues. In normal increased venous pressure increases the flow of lymph. He stated:

The final effect of increased venous pressure (therapeutic (subdiastolic) level, is to lower oxygen tension in the tissues, and thereby create an oxygen want which must be satisfied, upon release of a cuff, by a reactive hyperemia. Venous compression in addition to doing what arterial stoppage does, creating in the tissues an oxygen want, raises the pressure in the capillaries while the venous hyperemia is going on and so confers whatever benefits may be derived from that act.

Leriche¹⁸ elaborated the theory that the effect of the femoral vein merely caused in effect could be accomplished as well by periarterial sympathectomy. Studying the mechanical action of venous ligation in dogs, he found an increase in arterial pressure after ligation, transient, gradually returning to normal within some minutes, that is, after the venous circulation had been reestablished. He noted that immediately after ligation there occurred an arteriolar-capillary stasis, then a peripheral vasoconstriction, with an increase of peripheral arterial pressure, and when the vein was released there was a sharp fall in pressure, due to active vasodilation. Section of the lumbar ganglia did not alter this phenomenon; furthermore, ligation

11. Theis, F. V.: Ligation of Artery and Concomitant Vein in Operations on Large Blood Vessels, *Arch. Surg.* 17:244 (Aug.) 1928.

12. Van Gorder, G. W.: High Vein Ligation in Thromboangiitis Obliterans: Report of Nine Cases, *Ann. Surg.* 90:88, 1929.

13. Brooke, R.: Peri-Arterial Sympathectomy with Ligation of the Femoral Vein in Treatment of Diabetic Gangrene, *Brit. J. Surg.* 15:286, 1927.

14. Spurrell, W. R.: Experimental Study of Circulatory Changes Following Ligation of Main Artery and Vein to Hind Limb, *Guy's Hosp. Rep.* 80:20, 1930.

15. Lewis, T., and Grant, R.: Reactive Hyperemia in Man, *Heart* 12:73, 1925.

16. Collens, W. S., and Wilensky, N. D.: Treatment of Intermittent Venous Compression in the Treatment of Peripheral Vascular Disease, *Am. Heart J.* 1936.

17. Homans, J.: *Circulatory Diseases of the Extremities*, New York, The Macmillan Company, pp. 12-15.

18. Leriche, R., and Fontaine, R.: Mechanical Action of Venous Ligation in Arterial Obliteration, *Lyon chir.* 27:602, 1930.

vein in one extremity caused the same reaction in the other. He found that the desired therapeutic vasodilatation was accomplished in seven minutes to one hour, that is, as soon as the arterial pressure was stabilized.

Pearse¹⁹ studied a group of 20 cases of arteriosclerosis and diabetic gangrene in which he performed ligation of the femoral vein and noted the effect of this procedure on (a) the amount of pain, (b) the course of the gangrene, (c) the pulsation of the vessel and (d) the structural changes in color. He found that in 10 per cent of the cases there was definite improvement and in 40 per cent amputation was needed in one year after ligation. He concluded that ligation of the femoral vein is indicated in those borderline cases in which there is evidence of severe but not hopeless arterial damage and occlusion and clinical evidence of impending gangrene. McWhorter²⁰ ligated both the femoral artery and the femoral vein in a small group of cases of thromboangiitis obliterans and stated the belief that the results were beneficial.

Silbert²¹ performed ligation of the femoral vein in 16 cases, 8 of which were instances of thromboangiitis obliterans and 8 of arteriosclerosis. Twenty-four hours after operation, he noted a rise in temperature of the limb, a subjective feeling of warmth in the limb, frequently a dramatic relief of pain and slight swelling of the leg with some distention of the superficial veins. He concluded that ligation of the femoral vein had a definite, though limited value in the treatment of chronic occlusive arterial diseases.

Wilson²² in England repeated some of the experiments on animals that had previously been performed dealing with venous ligation in cases of arterial occlusion and disagreed with the impressions derived by other investigators. His conclusions were as follows: 1. A rise in the arterial and the venous pressure may occur, but the arterial pressure lasts only twelve hours. 2. The rise in arterial pressure does not depend on the effects of sympathetic innervation or release. (This disputes the theory of Leriche.) 3. The procedure did not affect the incidence of gangrene in his series of cases. 4. There may

occur a richer collateral bed as a result of ligation, but it has no bearing on the nutrition of tissues or on the process of gangrene. 5. Ligation of the femoral vein may produce the dangerous effects of chronic venous stasis. 6. If the principle of venous ligation is to be practiced at all, temporary occlusion would be preferable.

Brooks, Johnson and Kirtley²³ sought to determine by experimental means the exact conditions constituting indications for ligation of the femoral vein following arterial obstruction. They repeated the work of Brooks and Martin⁵ on rabbits, with the following results: In 100 experiments the arteries alone were ligated, with mass necrosis of the extremity resulting in 46 animals; in 100 experiments in which concomitant ligation of the vein was done with ligation of the artery, necrosis occurred in only 4 rabbits. However, when the arteries were injected with a radiopaque substance, there was not the same degree of arterial obstruction in any 2 rabbits. It was therefore difficult to evaluate by arteriographic evidence the changes occurring after ligation. They concluded that ligation of the vein had an extremely favorable influence on the incidence of gangrene but that the proof must rest essentially on clinical evidence.

Ligation of the femoral vein proximal to the saphenofemoral junction causes temporary edema. A small degree of this swelling may be due partly to reflex vasospasm and when recognized may be amenable to lumbar ganglion block with procaine hydrochloride. In my experience, ligation immediately distal to the junction of the vena profunda with the superficial femoral vein is free from subsequent edema. However, the degree of residual edema may be dependent on the presence or absence of venous thrombosis, which may have been present before the venous ligation or may have occurred afterward. Edema is also dependent on the number of functioning collateral vessels as noticed after ligation of the inferior vena cava, which in most instances is attended by less edema than when the common femoral vein is interrupted. The reason for this is evident in a review of the anatomy of the collateral veins in this region. Disagreement on this point by some can be traced to varied levels employed in ligation of the femoral vein. Silbert,²¹ who practiced ligation of the common femoral vein, noted swelling on the day following operation. It was moderate and tended to

19. Pearse, H. E., Jr.: Use of Vein Ligation in Treatment of Arteriosclerotic and Diabetic Gangrene, *J. A. M. A.* 98:866 (March 12) 1932.

20. McWhorter, G. L.: Ligation of Both Femoral Artery and Vein in Thromboangiitis Obliterans, *S. Clin. North America* 10:283, 1930.

21. Silbert, S.: Value of Femoral Vein Ligation in Chronic Arterial Obstruction, in Contributions to the Medical Sciences in Honor of Dr. Emanuel Libman, New York, International Press, 1932, vol. 3, p. 1079.

22. Wilson, W. C.: Occlusion of Main Artery and Main Vein of a Limb, *Brit. J. Surg.* 20:393, 1933.

23. Brooks, B.; Johnson, G. S., and Kirtley, J. A., Jr.: Simultaneous Ligation: Experimental Study of Effect of Ligation of Concomitant Vein on Incidence of Gangrene Following Arterial Obstruction, *Surg., Gynec. & Obst.* 59:495, 1934.

diminish. He stated that "some increase in the size of the leg occasionally persists, but has never been more than a few centimeters and has caused no discomfort or complaints." Homans²⁴ aptly summarized the resulting edema as follows:

It should be recognized that whereas division of the superficial femoral vein for thrombosis confined to some group of deep veins below the knee is attended by little or no edema and cyanosis, the situation when the whole femoral system is occupied is very different; collateral pathways are perhaps involved, and division may cause serious edema.

Allen, Linton and Donaldson,²⁵ although they agreed that ligation of the femoral vein is a simple and effective procedure, stated that edema is the most common and most serious postoperative complication but may usually be controlled by the application of a woven bandage. Early swelling is more frequent after ligation of the common femoral vein, but late edema occurs with equal frequency after either superficial or common femoral interruption. In Veal's²⁶ cases, following amputation edema of the stump occurred only occasionally. He explained this complication as probably due to thrombosis in the profunda vein. However, even in these instances the edema subsided within ten days.

The experience with this series that there has been complete absence of pulmonary complications following ligation of the femoral vein, especially when amputation was performed subsequently, has been corroborated by Veal. He noted that pulmonary embolism has always been a common and dreaded complication following amputations on the thigh. By performing a prophylactic ligation of the femoral vein at the time of amputation, Veal has reduced this complication to almost zero. Of 275 cases of amputation without the benefit of ligation of the femoral vein, death due to pulmonary complications occurred in 14.9 per cent, while in 80 cases of amputation with ligation there was only 1 pulmonary complication. This low incidence is explained by the fact that the femoral vein below the vena profunda commonly receives only a few small branches, so that a low ligation would

leave a column of blood with a sluggish circulation. With only a few small tributaries an ascending clot might easily break off; level, where the caliber of the femoral vein is increased.

Relief of pain following ligation of the femoral vein in the majority of the cases was in our preliminary report. Relief of pain resulted not only of increased collateral circulation with its attendant increased oxygenation of tissues. Division of the femoral vein rarely includes partial interruption of its collateral pathways. This is also a probable relief of pain. In addition, there is another factor, as yet not understood, explained as has been illustrated in cases of thromboangiitis obliterans in which there is relief of pain following ligation of the superficial femoral vein. This observation was made in 4 cases and also in 1 case of arteriosclerosis. In view of these findings, it might be expected to see whether ligation of any isolated vein would not give identical results.

My technic for performing ligation of the femoral vein consists of interruption of the superficial femoral vein immediately distal to its junction with the vena profunda. The ligature, 4 inches (10 cm.) in length, is placed in the course of the femoral artery starting at the inguinal ligament. Transfixion of the cut end of the vein is a safeguard against slipping of the ligature.

ANALYSIS OF CASES

As might be expected, the condition of the patients without exception was complicated by systemic degenerative disease. This includes 110 patients subjected to 118 operations of the femoral vein—bilateral for 8 cases. Lesions on the feet or toes, such as ulcers, gangrene or cellulitis, were present in 88 (75 per cent) of the patients, outlined in table 1. The principal diagnoses made on the patients on admission to the hospital under the heading of peripheral vascular disease were arteriosclerosis

TABLE 1.—Incidence of Lesions on the Feet and Toes

	Ulcers on Toes	Cellulitis	Molting Gangrene of Toes
Diabetes with arteriosclerosis.	17	7	7
Arteriosclerosis obliterans.....	8	2	6
Thromboangiitis obliterans...	1	0	0

24. Homans, J.: Exploration and Division of the Femoral and Iliac Veins in the Treatment of Thrombophlebitis of the Leg, *New England J. Med.* **224**:179, 1941.

25. Allen, A. W.; Linton, R. R., and Donaldson, G. A.: Thrombosis and Embolism: Review of Two Hundred and Two Patients Treated by Femoral Vein Interruption, *Ann. Surg.* **118**:728, 1943.

26. Veal, J. R.: The Prevention of Pulmonary Complications Following Thigh Amputation by High Ligation of Femoral Vein, *J. A. M. A.* **121**:240 (Jan. 23) 1943; High Ligation of the Femoral Vein in Amputations of Lower Extremities, *ibid.* **114**:1616 (April 27) 1940.

complicated by diabetes (60 cases), arteriosclerosis obliterans (44 cases) and thromboangiitis obliterans (6 cases). The associated diseases served on the patients' admission are listed

e 2. The sex incidence was 43 women and men. Of these, 60 were diabetic—33 women 27 men. The age incidence showed the greatest number of persons to be in the sixth decade—the youngest was 33 and the oldest 92 years (table 3). In addition to the operative procedures outlined in table 4, 30 amputations of the thigh were performed subsequent to ligation of the femoral vein. The lapse of time after the latter operation was one to two hundred and twenty days. Ten patients in this series

could not be traced. As analyzed in table 6, the end results are divided according to the age group and the interval following ligation of the femoral vein.

TABLE 2.—Associated Diseases Observed on Hospitalization

	No. of Cases		No. of Cases
Monary tuberculosis.	2	Cardiac decompensation....	8
ricular fibrillation....	6	Iliofemoral thrombophlebitis	4
physema.....	10	Lymphogranuloma venereum	1
erial thrombosis....	6	Hemiplegia.....	9
ronary thrombosis...	11	Asthma.....	5
urisy.....	2	Cirrhosis of liver.....	8
pbills.....	9	Carcinoma of rectum.....	1

TABLE 3.—Peripheral Vascular Diseases According to Age Distribution

	Age Groups							
	30-39	40-49	50-59	60-69	70-79	80-89	90-99	
Diabetes with arterio-								
sclerosis.....	1	2	14	25	13	2	0	
Arteriosclerosis oblit-								
erans.....	0	1	9	14	16	4	1	
Thromboangiitis oblit-								
erans.....	2	1	2	1	0	0	0	

TABLE 4.—Additional Operative Procedures

	No. of Cases
Amputation of toe.....	15
Excision and drainage.....	11
Periarterial sympathectomy	45
Ligation of femoral artery.....	2
Lumbar ganglionectomy	6
Excision of femoral artery.....	1
Neurectomy for pain.....	5
Excision of infected callus.....	4
Arteriography	24

were admitted with a previous amputation on the thigh. Pain as a prominent symptom on admission was noted in 61 patients. Relief for 50 (81.9 per cent) resulted following ligation of the femoral vein. The mortality in the hospital was in no instance associated with ligation of the vein. An analysis of the 20 deaths in this series (table 5) are attributed to intercurrent diseases.

An attempt at follow-up examinations in this series was successful for 75 of the 90 patients who were discharged from the hospital—15

TABLE 5.—Analysis of Twenty Deaths Occurring in the Hospital

Age	Postoperative Days	Cause of Death
60	60	Pneumonia and nephrosis
75	46	Uremia
63	60	Coronary thrombosis
63	3	Coronary thrombosis
67	5	Coronary thrombosis
79	41	Cardiac decompensation
72	7	Sepsis—refused operation
76	55	Cerebral embolism
56	30	Pneumonia—tuberculosis
64	12	Cerebral thrombosis
82	15	Cerebral thrombosis
65	25	Coronary thrombosis
50	5	Cerebral thrombosis
70	46	Sepsis—refused amputation
78	86	Sepsis—refused amputation
51	5	Uremia
74	30	Sepsis—refused amputation
57	65	Sepsis—refused amputation
62	13	Cardiac decompensation
74	12	Cardiac decompensation

TABLE 6.—Data on Follow-Up Examinations in Seventy-Five Cases

Age Group	Postoperative Interval in Years	No. of Cases	Result
30 to 39	5	1	Alive and well
	3	1	Alive and well
	2	1	Amputation—thromboangiitis obliterans
40 to 49	4	1	Alive and well
	4	1	Alive and well
	4	1	Alive and well
	2	1	Alive and well
50 to 59	5	9	Amputation for 2; 7 alive and well
	4	3	Amputation for 1; 2 alive and well
	3	1	Amputation
	2	5	Died of "heart disease"
	1	1	Died of sepsis—amputation refused
60 to 69	5	4	Amputation for 2
	4	2	Alive and well
	3	8	Amputation for 3
	2	8	4 died—"heart disease"; 4 had sepsis and gangrene
	1	6	5 died—"heart disease"; 1 had sepsis and gangrene
70 to 79	4	4	Amputation for 1
	3	2	Amputation for 1
	2	4	4 died—"senility"; 1 had sepsis and gangrene
	1	4	2 died—"senility"; 2 had sepsis and gangrene
	1	1	Alive and well; 1 died—"senility"
80 to 89	2	2	Died—sepsis and gangrene
	1	2	2 died after amputation
92	1	1	Died—"senility"

COMMENT

In accordance with physiologic principles and clinical experience, ligation of the femoral vein is a valuable procedure in selected cases, as discussed in the previous review of the literature and the

ligatures done in the Flower and Fifth Avenue Hospitals and the Metropolitan Hospital. In order to determine indications for the procedure and a proper selection of cases, ligation of the femoral vein was performed on all patients with chronic obstructive arterial disease who consented to the operation. As a result, the series included patients whose condition was unfavorable or "hopeless" in view of such complications as spreading gangrene and sepsis. However, ligation of the femoral vein was of definite value in the prevention of gangrene and the alleviation of pain. Increased collateral circulation was evidenced by increased bleeding which was noted at amputation following ligation of the femoral vein and also by means of arteriography. In 6 of the patients, the pulses became palpable postoperatively. The absence of pulmonary embolism as a complication following amputation has also been noted. Ligation distal to the entrance of the profunda vein is probably the reason why edema was absent in these patients. Thrombosis has never been noticed in the femoral vein proximal to the site of ligation because large tributaries in this region associated with a swift stream of venous blood obviate this complication. Final follow-up examinations of those patients who were found alive (38.6 per cent, or 29 patients) showed that of these 17 required amputation. In this group, 14 had been admitted to the hospital with gan-

grene or ulcers on the toes, while of those who remained alive and well 8 had been hospitalized with these same lesions. In other words, 10 of the 110 patients were admitted with lesions on the toes; this showed that the number of patients were treated after in which ligation of the femoral vein was considered prophylactic. However, 38.6 per cent of the entire series were alive at the final follow-up examination. It is reasonable to expect that had ligation of the femoral vein been performed as a preventive measure only, the statistical figures would have been more impressive. Since no mortality is associated with the procedure of ligation of the femoral vein this operation should be employed more commonly in selected cases as suggested previously.

SUMMARY

Ligation of the femoral vein is definitely indicated for prophylaxis in chronic obstructive arterial disease—before such lesions as ulceration and infection present themselves.

Ligation of the femoral vein is not associated with morbidity or mortality.

Relief of pain was obtained in the majority of the cases.

The prevention of subsequent pulmonary embolism following amputation is definite.

TESTICULAR TUMORS

MAJOR VINCENT VERMOOTEN

MEDICAL CORPS, ARMY OF THE UNITED STATES

During the past two years, 62 soldiers with testicular tumors were admitted to the Brooke General Hospital for treatment. A statistical analysis of this rather large series of tumors has been made, the results of which stress the need for careful and routine examination of the scrotal contents. The difficulty of differentiating by physical examination alone between a benign and malignant growth involving the testis is also emphasized.

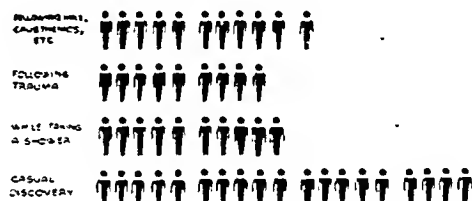
INCIDENCE

In civilian practice testicular tumors are encountered rather infrequently. Hinman and Smith¹ stated that they are rare and comprise only about 0.57 per cent of all malignant tumors, while Dean² claimed that they "constitute 2.09 per cent of all malignant tumors in the male." In contrast, it was found that "testicular tumors constituted 7.2 per cent of all malignant neoplasms occurring in white enlisted personnel of the United States Army for the calendar year 1941."³ This difference is great, even when one takes into consideration the age of the army personnel. There seem to be several factors associated with the routine of army life which may contribute to this marked difference in incidence.

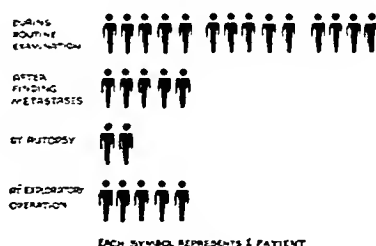
In analyzing the case histories of the 62 patients with tumors of the testis in this series, it was found that 10 of the tumors were accidentally discovered by soldiers while they were soaping themselves in a shower bath. Hikes, calisthenics, participation in events on obstacle courses and other military training drew the attention of 11 other soldiers to the presence of large, swollen or painful testes, which later proved to be due to tumors. Fourteen of the 62 tumors were discovered incidentally by medical officers while they were doing routine physical examination. On

the other hand, only 9 were discovered as the direct result of trauma. In some instances, the soldier knew that his testis was large, hard or heavy, but, as it had not bothered him, caused him any pain or in any other way interfered with his duties, he had not reported the fact. Thus, were it not for the routine physical examinations and the routine of army life, the early treatment of 35 of these 62 tumors, excluding the 9 associated with direct trauma, might have been considerably delayed (chart 1).

DISCOVERED BY PATIENT



DISCOVERED BY MEDICAL OFFICER



EACH SYMBOL REPRESENTS 1 PATIENT

Chart 1.—Chart to illustrate how the testicular tumors were discovered.

TRAUMA

These observations also draw attention to the relationship of trauma to tumor. For only 16 tumors was there a history of either recent or remote trauma, while for 46 no such history could be elicited. Fourteen tumors were found on routine examination by a medical officer, 10 were discovered by the soldier while taking a shower and 11 were noticed after the hard physical effort of outdoor army life caused symptoms such as pain or swelling. Thus in this series 35 of the 62 tumors were present and unknown to the soldier. It would be reasonable, therefore,

From the Urological Section of the Surgical Service, Brooke General Hospital, Fort Sam Houston, Texas.

1. Hinman, F., and Smith, D. R.: Tumors of Testis, *J. Med.* 22:393 (Nov.) 1941.

2. Dean, A. L., quoted by Lowsley, O. S., and Kirwin, T. J.: *Clinical Urology*, Baltimore, Williams & Wilkins Company, 1944.

3. Testicular Tumors, News and Comment, *Bull. U. S. Army M. Dept.*, April 1944, no. 75, p. 34.

to assume that the 9 tumors associated with direct recent trauma must have been present at the time of injury and that the injury, like the shower bath, merely directed the patient's attention to his scrotal mass. Except for that, there is no possible direct etiologic relationship between the trauma and the tumor.

Some authors have expressed the opinion that frequently repeated trauma to an undescended testis accounts for the greater incidence of tumors in undescended than in normally descended testes. However, in 1 of my patients an embryonal carcinoma developed in an intra-abdominal testis; in another, a man of 39, a similar tumor developed in a scrotal testis which had not descended until the age of 10 years, when spontaneous descent occurred, while in a third a malignant teratoma developed in a testis for which an orchidopexy had been successfully done thirteen years previously. The greater frequency of tumors in undescended testes would, therefore, seem to be not so much the result of trauma but associated with some congenital malformation, which in itself may play a part in the lack of normal descent.

This is further emphasized by Hamilton and Gilbert,⁴ who pointed out not only the greatly increased incidence of tumors in undescended testes but the still far greater incidence of tumors occurring in abdominal testes, in which the factor of trauma can be entirely excluded.

DIAGNOSIS

The difficulty of diagnosis, which was pointed out so well by Gilbert⁵ in 1942, is also illustrated in this series of tumors (chart 2). Of the 62 tumors, 1 was originally diagnosed as a varicocele, 1 as an enlarged testis, 6 as hydroceles and 5 as traumatic orchitis; but the largest number, 14, were incorrectly diagnosed as epididymitis, orchitis or epididymo-orchitis. Either because of the chronicity of the disease or because of lack of fever, pain, redness and other symptoms of an acute lesion, many were qualified as tuberculous. Despite these incorrect initial diagnoses, all of the patients with 1 exception were operated on within four months from the time the lesion was first seen by a medical officer. Forty-two, or 82.3 per cent, of the patients with malignant tumors were operated on before the end of the second month after they first sought medical advice.

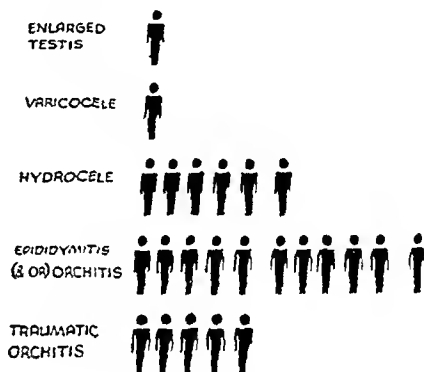
4. Hamilton, J. B., and Gilbert, J. B.: Studies in Malignant Tumors of Testis: Bilateral Testicular Cancer, *Cancer Research* 2:125 (Feb.) 1942.

5. Gilbert, J. B.: Pitfalls in Diagnosis of Testis Tumors, *M. Times*, New York 70:85 (March) 1942.

BENIGN LESIONS

Of the 62 lesions which were clinically nosed as testicular tumors, 11 proved benign. One of these was an adult being a cystic structure and containing striped muscle and glandular elements

CASE 1.—The patient gave a history of twelve years previously, followed by scrotum, for which an operation for hydrocele a year later. Five months before his admission to hospital, he was again struck on the same side by a subsequent swelling, for which, three months later, he was admitted to the hospital. At this time, an operation for recurrent hydrocele was made, aspiration and the soldier returned to duty. As a result of the recurrent increase in the size of the testis, he was hospitalized two months later. The testis had increased to ten times the size of the normal structure felt cystic but could not be seen by illumination. The spermatic cord was thick and not nodular. Despite the absence of metastases, the negative reaction to the Friedman test, or



EACH SYMBOL REPRESENTS 1 PATIENT

Chart 2.—Chart giving original diagnoses, to illustrate the difficulty in making an accurate diagnosis when the patient first complains of symptoms; each symbol represents a patient.

was performed in October 1943. A prophylactic course of deep roentgen therapy was given, and the patient was returned to duty.

A second benign tumor was found on the left testis to be a cavernous hemangioma of the testis.

CASE 2.—A 20 year old soldier gave the following history: In 1938 he had pain in the right testis followed by swelling for two to three hours. Later he had a similar attack of pain, but this time there was no appreciable change in the size of the testis. On Dec. 8, 1943, he was awakened at 3 a.m. by severe pain, for which he was admitted to the hospital. During the next forty-eight hours he had fever and the scrotal content increased to the size of a large orange. He was given sulfathiazole, and an incision was applied to the scrotum. His condition improved and the swelling gradually subsided. He was discharged a month later. There was no history of injury and no evidence of tuberculosis. After doing duty for two weeks he was called back to the sick call, because his testis was hard and he had

othered" him. On examination, the right testis was found to be barely twice normal size (as compared with the left), but it seemed to be almost entirely replaced by a hard, smooth, heavy organ. It was not possible to feel the epididymis separate from the testis. No clinical evidence of hydrocele was present. The scrotum was normal. The patient was admitted to the hospital with a clinical diagnosis of tumor of the testis. This diagnosis was concurred in, and orchiectomy was performed. On section, a cavernous hemangioma was found within the tunica albuginea, which replaced about one third of the testis.

CASE 3.—A 22 year old soldier was admitted to the hospital three months after he discovered, while taking a shower, that his left testis was large. He had had no injury, but owing to the progressive increase in the size of the testis and the onset of pain he eventually sought medical aid. On examination, the left testis was observed to be three to four times the size of the right; it gave a sensation of weight but was smooth and well shaped and felt like a soft hydrocele. However, because it was not translucent and because the epididymis could be felt, a diagnosis of hydrocele could not be made; consequently, exploratory operation for tumor was advised. At operation, the testis was seen to be about four times normal size and extremely soft and mushy, as though the entire testicular substance were necrotic and liquefying. Without opening the tunica albuginea, orchiectomy was performed, and later, on section, the testis was found to have undergone coagulative necrosis." Another testis which was similarly removed contained a small interstitial cell tumor.

Among the other benign tumors operated on was a dermoid cyst which was found within the tunica albuginea of the testis. None of the benign tumors could be differentiated on clinical findings alone from malignant growths; consequently I feel that it is extremely unwise for a physician to give high voltage roentgen or radium therapy to a patient because he thinks he can by clinical examination alone make a correct diagnosis.

MALIGNANT TUMORS (CLINICALLY OBSCURE)

In 1 of the patients with clinically obscure malignant testicular tumor the primary lesion was not found until autopsy, despite previous careful examination of the scrotal contents.

CASE 4.—The patient was admitted to the hospital with a large "retroperitoneal sarcoma," which grew locally in size and eventually killed the patient without any metastatic spread. He had had epididymitis six months before admission, and during his stay in the hospital the old healed epididymal lesion was recognized, but the testes were normal in size and consistency. At autopsy a malignant teratoma, measuring 5 cm. in diameter, was found within the left testis.

CASE 5.—Another patient was admitted to the hospital with pulmonary metastasis, which appeared to be either testicular or renal in origin. Pyelograms were normal, and the testes were thought to be normal when palpated, even with the knowledge that one or the other must contain a malignant growth. On the basis of a history of traumatic orchitis on the right side two months previously, an orchiectomy was performed on that side. On section, a tumor less than 1 cm.

in its greatest diameter was found within the testis. Microscopically, this was seen to be a malignant teratoma.

In addition to these patients, 5 others were admitted to the hospital because of the finding of metastasis, which later led to the discovery of the primary testicular lesion.

METASTASIS

In this series, only 15 of 51 malignant tumors showed evidence of metastasis when the patient was first admitted to the hospital, and 2 of these 15 showed no clinical evidence of the primary lesion. This incidence of only 30 per cent of tumors with clinical evidence of metastasis at the time of hospitalization is in sharp contrast to that in Hinman's⁶ series of 80 tumors in which 41 showed evidence of metastasis. Unquestionably, several other tumors must have undergone metastasis which was not clinically demonstrable at the time of admission, for in at least 3 patients recognizable metastasis developed while the patients were receiving treatment. This lowered incidence must, in great part, be due to the fact that soldiers have easy access to medical advice and to frequent routine physical examinations.

TREATMENT

After a careful history concerning the nature and development of the scrotal lesion has been obtained, a careful physical examination done and a diagnosis of malignant tumor of the testis arrived at, orchiectomy or, in occasional questionable cases, an exploratory operation should be performed without further delay and without preliminary roentgen or radium therapy. This should be done principally to establish a correct and accurate diagnosis, for in my experience it has not been possible in several instances to establish the correct diagnosis in any other way. Without primary operation several of the patients with benign lesions might have been treated as though they had cancer.

I consider effective and efficient irradiation a serious matter, for it must do a certain amount of permanent injury or damage to normal tissues. Furthermore, orchiectomy should be done as a radical and not as a minor scrotal procedure.

A. Technic of Radical Orchiectomy.—The incision extends from the level of the external inguinal ring to above the internal ring. The aponeurosis of the external oblique muscle is split from the external ring upward. The internal oblique muscle is then separated from the cord, and the cord is dissected up to beyond the point where the vas deferens and the vascular

6. Hinman, F., cited by Taylor, G. W., and Nathanson, I. T.: *Lymph Node Metastases*, New York, Oxford University Press, 1942.

portion of the cord separate. The adherent peritoneum is stripped off the cord, and the cord is ligated and divided as high as possible. The vas deferens is then pulled up, ligated and divided. Only then should the cord be dissected down to the external ring and the testis with all its tunics removed from the scrotum. If the tumor is small, it may be delivered through this incision. If it is large, it is preferable to make a scrotal incision through which to deliver the testis and the cord. This avoids all manipulation except that which is absolutely necessary.

High ligation of the cord is essential for several reasons. First, any early extension up the lymphatics is removed. Secondly, the possibility of a local recurrence is greatly reduced; thirdly, should there be any tumor at the site of the division of the cord, the recurrence will grow as an intra-abdominal mass, which will not distress the patient as would a fungating mass in the wound.

B. *Technic of Scrotal Exploratory Operation.*

—In occasional instances in which there is reasonable doubt as to the nature of the testicular tumor, an exploratory operation may be done. This consists of a scrotal incision carried directly down through the tunica vaginalis without any dissection. Through this incision, the testis can be delivered into the wound. If the tumor is found to involve the testis, the previously described radical procedure is carried out. If it proves to be an old thick-walled hydrocele, an organized hematocele, a tumor of the tunica vaginalis or epididymis or some similar lesion, the testis may be preserved. If the surgeon feels it is necessary to open the tunica albuginea either with a scalpel or with a needle for diagnostic purposes, he would be well advised to do an orchiectomy and let the pathologist do any further exploration. Testicular tumors, as a group, are too malignant and spread too easily and rapidly for one to risk disseminating them. Exploratory operations, except in unusual circumstances, are consequently not recommended. It is far preferable to do an orchiectomy for a benign lesion than to disseminate a malignant one by meddlesome surgical intervention.

Whether there is clinical evidence of metastasis or not, the orchiectomy should be followed within a week by a course of high voltage roentgen therapy to the abdominal lymph nodes

along the normal course of spread up to including the periaortic lymph nodes on to in the region of the renal vessels.

Radical excision of the abdominal nodes was not carried out on any of my

RESULTS

Of the 51 patients admitted to the hospital with malignant testicular tumors, 11 are still living with metastasis, while 3 per cent. are alive without clinical evidence of metastasis. Of these 36, 16 have been alive a year to twenty-five months following operation. I am inclined to feel that the low incidence of metastasis is due to early diagnosis. Early diagnosis is favored by the routine of army life. Hikes, calisthenics and bat training make a soldier aware of the possibility of a tumor. So, too, do regular show-ups and much credit must be given to the careful routine physical examinations.

SUMMARY

A statistical analysis of a series of 62 testicular tumors seen during a two year period in a hospital indicates that there is a greater incidence of this type of lesion in army personnel among civilians; however, it is felt that due to the easy access which a soldier has to medical advice, to the frequent routine physical examinations and to the fact that a physically fit and active man is especially likely to notice an enlarged, hard or painful testis.

Trauma, except for drawing the soldier's attention to the tumor, bears no etiologic relationship to the lesion.

A testicular tumor when first seen is frequently mistaken for some other lesion. The most common diagnostic error is to consider the tumor as epididymitis, orchitis or hydrocele.

Eleven, or 18 per cent. of the tumors, are benign.

Radical orchiectomy, as described in this report, followed by immediate high voltage roentgen therapy resulted in 36, or 72 per cent. of 51 patients who were admitted to the hospital with malignant testicular tumors being alive without clinical evidence of metastasis. Of these 36, 16 have been alive from one year to twenty-five months following operation.

53525

EARLY REPAIR OF NEURAL WOUNDS WITH PENICILLIN THERAPY

COMMANDER NATHAN C. NORCROSS (M.C.), U.S.N.R.

The longer a damaged nerve is left unrepaired the less is the chance of there being a satisfactory end result. Primary suture is of course desirable, but under wartime conditions is rarely possible. Even though it has been found that some time, as measured in weeks, or even in a few months, can lapse before the end result is effected in a measurable degree, it seems desirable to keep the time element to a minimum; his has been done during the past two and one-half years.¹ The decision whether surgical intervention is necessary during this early period is difficult to make, and a thorough knowledge of the physiology of the nerve and of the clinical manifestations of disordered function is of paramount importance. Various features of this problem will be dealt with in later communications, but briefly they are those set down by Finel years ago.²

Recently, in a large base hospital, it has been possible to treat patients with neural wounds within a few days after the injury. Because some of the patients complained of severe pain, it was decided to give them penicillin therapy and to operate on them shortly after their admission to the hospital, in spite of infection.

Two groups of patients have been treated in this way: men whose wounds were healing by primary intention without infection and men whose wounds were still open and showed varying degrees of infection. For no patient with acute inflammation of the wound was this treatment attempted. To patients with apparently clean wounds, penicillin was given for two days before operation and for six to eight days afterward in doses of 10,000 units intramuscularly every three hours. To the other group (patients with infected wounds) penicillin was given for

four days before and for ten or more days after operation in doses of 20,000 units every three hours. These dosages have been found satisfactory, although they have been varied from time to time in individual cases. Local instillation of penicillin solution was used in 2 cases, while in most of the others the wound was dusted with sulfanilamide before closure.

REPORT OF CASES

CASE 1.—D. C. W. was struck by a fragment of a bullet in the upper portion of the right arm. After this his fingers stiffened and became numb. He was evacuated to an aid station, where the fragment of lead was removed from under the skin posterior to the wound through a surgical incision, and both wounds were dressed without suturing. During the evening of the day on which he was injured he started to have severe pain in the hand, which continued. This pain was deep and not well localized and was aggravated by noise or by movement. Examination on his admission to the hospital, two days after the injury, showed two longitudinal lacerations on the medial aspect of the right arm, both about $2\frac{1}{2}$ inches (6 cm.) long. Their edges were well approximated and dry. There was partial motor paralysis of the right median nerve, and superficial sensation in the distribution of this nerve was lost. Deep pain sense was retained. There was marked tenderness over the course of the nerve from the level of the wound to the wrist. Administration of penicillin was started on the day after hospitalization, and four days later, seven days after the injury, because of continued severe pain, operation was undertaken. The edges of the original wound were trimmed back to healthy tissue: the median nerve was exposed and found to be cut two thirds of the way through. This area was resected, with sacrifice of about $\frac{1}{2}$ inch (13 mm.) of the nerve. When this was done, degenerated tissue, myelin, etc., came out of the cut ends, both proximal and distal, like tooth paste. This degeneration allowed the sheath to collapse and made approximation rather difficult. An end to end anastomosis was carried out with interrupted sutures of fine silk, and the wound was closed in layers with interrupted sutures of fine stainless steel wire. Several similar sutures were placed in the skin of the other incision. The elbow was bent to 90 degrees, to relieve tension on the anastomosis, and a plaster splint was applied. Administration of penicillin was continued until the second postoperative day, when it had to be stopped because of a febrile reaction.³ Sulfadiazine was then given in its place for six days. The wound healed by first

3. During this period there were several febrile reactions to the penicillin, which were believed to be due to impurities in the preparation used.

This is the second of a series of communications on injuries of the peripheral nerves.

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writer and are not to be construed as reflecting the policies of the Navy Department.

1. Norcross, N. C.: Operative Experiences on Wounds of Peripheral Nerves from the Pacific Combat Area, *Bull. Am. Coll. Surgeons* 28:127 (June) 1943.

2. Finel, J.: *Nerve Wounds*, London, Baillière, Tindall & Cox, 1917.

intention. Three weeks after the operation the elbow was partially extended and was further extended slightly every few days for two and one-half weeks. Five and one-half weeks after the operation the arm was straight, and Tinel's sign had progressed to a point 2 inches (5 cm.) below the site of the suture. The neuritic pain was considerably lessened but not relieved entirely.

Because of the difficulty in suturing the nerve sheath during the active stage of wallerian degeneration, it was decided not to operate so early again. However, I can see no other reason to contraindicate early operation, and the rapid advance of Tinel's sign is intriguing.

CASE 2.—R. V. was admitted to the hospital eight days after he had been wounded, having been hit by a metal fragment in the back of the right thigh. His leg quivered and buckled under him, and he had severe pain running down to the foot. Four days after the injury an unsuccessful attempt was made to remove the fragment. Examination showed a 4 inch (10 cm.) wound in the posterior part of the right thigh, which was packed with petrolatum gauze. When this gauze was removed, a considerable amount of watery pus escaped. He had almost complete paralysis of the sciatic nerve below the level of the lesion and complete drop foot. He had had neuritic pain constantly since the injury. Administration of penicillin was started and continued for four days, by which time there was almost no drainage. The pain was, if anything, worse, and operation was therefore considered advisable. Twelve days after the injury he was operated on. The edges of the wound were trimmed back to healthy tissue, and a small portion of muscle badly contused was excised. The sciatic nerve was exposed and observed to be surrounded and constricted by scar but not otherwise damaged. The metal fragment was not easily accessible and was not removed. The wound was thoroughly irrigated, penicillin solution instilled and the

wound closed without drainage in interrupted sutures of stainless steel wire administered for six days, at which time it was discontinued because of a febrile reaction. The wound healed by first intention, without any evidence of infection. Some return of function was noted the first postoperative day, and improved steadily until the patient's transfer, six weeks after operation. The neuritic pain was considerably lessened but was not eliminated.

COMMENT

Ten additional patients have been treated in a similar manner from twelve days to three months after the original injury; 3 had an average of 7 neurolyses. All wounds healed by first intention, without complications. In 2 cases in which the ulnar nerve was sutured, the wound granulated, but apparently clear of infection. Penicillin was given because of misadventure of orders in the ward, but in this case no infection occurred without complication.

These early operations were originally taken in an attempt to relieve the pain and to minimize the trophic changes which may result from early severe neuritic disturbances. It is difficult to judge whether or not this goal has been attained, although the early results are encouraging. They do demonstrate, however, that prophylactic or suppressive penicillin in the treatment of traumatic surgical treatment can be carried out on neural wounds much earlier than has previously been deemed advisable.

CONVULSIVE FACTOR IN COMMERCIAL PENICILLIN

A. EARL WALKER, M.D.,* AND HERBERT C. JOHNSON, M.D.

WITH THE TECHNICAL ASSISTANCE OF WILLIAM H. FUNDERBURK, B.S.

CHICAGO

Reports on intrathecal administration of penicillin in treating infections of the central nervous system are becoming numerous. Recently intraventricular injection of penicillin has been employed when meningitis did not respond to parenteral or intrathecal modes of administration.¹ The direct application of penicillin to wounds of the cerebral cortex in the treatment of injury to the head has also been suggested.² Our interest in the effect of penicillin on the central nervous system was aroused by observing convulsive seizures following intraventricular injection of the drug in a case of ventriculitis.³ Experiments were then planned to investigate the effect of the drug when administered intracisternally, intraventricularly and locally to the cerebral cortex either by application to the subdural space or by intracortical injection. Such experiments were performed, and it was observed that certain doses of penicillin so administered to mice, cats, dogs and monkeys gave rise to convulsive manifestations. This report deals particularly with the effect of commercial penicillin on the cerebral cortex.

METHODS AND MATERIALS

Some 11 monkeys and 19 cats were used repeatedly in this study. All operative procedures for chronic experiments were carried out aseptically with the animal under general anesthesia induced with pentobarbital sodium administered intraperitoneally.⁴ For acute experiments the animals were usually prepared under anesthesia induced by vinethene and procaine hydrochloride. For routine electroencephalographic studies curare was given to insure that muscular movements

Presented as a demonstration to the Central Neuro-psychiatric Association, Oct. 30, 1944.

*From the Division of Neurological Surgery and the Otho S. A. Sprague Memorial Institute, the University of Chicago.

1. McCune, W. S., and Evans, J. M.: Intraventricular Penicillin in the Treatment of Staphylococcal Meningitis, *J. A. M. A.* **125**:705-706 (July 8) 1944.

2. A Review of the Florey and Cairns Report on the Use of Penicillin in War Wounds, *J. Neurosurg.* **1**:201-210, 1944.

3. Johnson, H. C., and Walker, A. E.: Intraventricular Penicillin: A Note of Warning, *J. A. M. A.* **127**:217-219 (Jan. 27) 1945.

4. Dr. Jerry J. Kollros rendered technical assistance in the preparation of the animals.

should not introduce artefacts. Respiration was then maintained artificially. The electrodes used for obtaining the electroencephalograms were screwed into the calvaria and insulated from skin and muscle. The electrocardiogram was derived from needle electrodes inserted in the muscles of the two forelimbs. The amplifiers used for augmenting the electrocardiogram and the electroencephalogram were two-sided resistance-capacity-coupled machines with direct coupling between the last two stages, working into an ink-writing oscillograph.⁵

Commercial penicillin,⁶ made by seven different manufacturers in the form of sodium penicillin, was used; all specimens gave similar results. Routinely the penicillin was dissolved in sterile isotonic solution of sodium chloride, but other solvents have been used without greatly modifying the convulsive factor. In the acute experiments the penicillin solution, usually 0.05 cc., was injected into the subdural space through a trephine hole. In the chronic experiments a hypodermic needle was inserted through the skin and a trephine hole into the cerebral cortex. The absolute site of these injections could not be accurately gaged because of the varying thickness of the animals' scalps and skulls, but an attempt was made to inject the penicillin solution, usually 0.05 cc., just beneath the dura mater.

An estimate of the antibacterial potency of the penicillin inactivated by various methods was made by the agar hole method suggested by Fleming.⁷

EFFECTS OF INTRACORTICAL INJECTION OF PENICILLIN

Both the cat and the monkey within five minutes of injection of 0.05 cc. of a solution containing 1,000 or more Oxford units of penicillin appeared listless and became uninterested in their surroundings. The cat frequently cried as if in distress. At times the animal exhibited evidences of sympathetic discharge, the pupils dilating, the back arching and the hair, particularly that of the tail, standing erect. Saliva sometimes drooled from the mouth. At about the same time the animal began to have quick myoclonic jerkings of the extremities or face

5. Dr. Theodore J. Case gave assistance with the electronic equipment.

6. The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for experimental investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

7. Fleming, A.: In-Vitro Tests of Penicillin Potency, *Lancet* **1**:732-733, 1942.

opposite to the site of injection. At first such jerks occurred every minute or two, but gradually they tended to become more frequent. The jerk was usually a flexion movement of the extremity but might be associated with abduction of a limb or rotation of the head. Whether the upper or the lower extremity was affected depended on the site of the injection into the cerebral cortex; an injection in the motor arm area of the cerebral cortex produced an attack that involved primarily the contralateral foreleg, and an injection in the motor leg area the contralateral hindleg. If the injection was made in the temporal region, twitching of the contralateral ear was the first evidence of the attack. If the injection was made in the prefrontal region the head and eyes turned to the opposite side, and the animal tended to exhibit circus movements.

After these manifestations had been present for ten or fifteen minutes the myoclonic twitchings became a series of jerks of increasing intensity, spreading at the same time to involve the remainder of the musculature on the side contralateral to the injection. With these attacks the animal might be thrown on its side. The animal appeared definitely ill even between the attacks and took little interest in its surroundings. These series of twitchings might last from a few seconds to a few minutes, and then they gradually or suddenly decreased. Such attacks after continuing for a minute or two might become generalized. The seizure then consisted of a long series of clonic movements of the forelegs and hindlegs, the jerking usually being more severe and more persistent in the extremities contralateral to the site of application of penicillin.

At the cessation of the attacks the animal might remain in a dazed or semicomatose state for several minutes. Then another attack started, first in the contralateral extremities but rapidly spreading to the entire body. Such convulsive seizures might continue for several hours. In fact, we have followed such epileptic states for as long as seven hours. Under these circumstances the animal rarely regained consciousness between the attacks but remained in a semicomatose state. The generalized attacks could ordinarily be controlled by intraperitoneal injection of 0.06 to 0.12 Gm. of phenobarbital sodium.

Convulsive Threshold.—In the cat intracortical injections of 10,000 to 20,000 units of penicillin regularly brought on generalized convulsive seizures. Smaller doses usually induced only contralateral twitchings of the extremities. In the monkey, however, the convulsive thresh-

old appeared to be definitely lower. In order to determine more accurately the convulsive threshold a series of 10 monkeys was prepared. The animals were operated on under aseptic conditions, burr holes being placed over the motor cortex on both sides and in the frontal region on both sides. After the animal had recovered from the operation, commercial penicillin was dissolved so that the desired amount could be injected into the cerebral cortex of each monkey in 0.05 cc. of isotonic solution of sodium chloride. In the first group of experiments each monkey received 2,500 units of penicillin. In 8 of 10 monkeys generalized convulsive attacks developed within a few minutes. One had local twitching of the opposite extremities but no generalized convulsive seizures. On other occasions the animals received injections of 1,000 Oxford units, 500 Oxford units and 250 Oxford units.

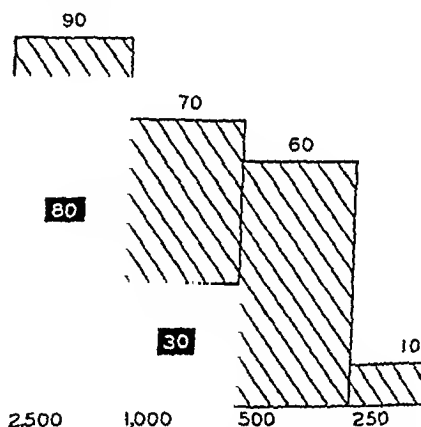


Fig. 1.—Histogram showing the percentage of monkeys in which convulsive manifestations developed after the intracortical injection of 2,500, 1,000, 500 and 250 Oxford units of penicillin dissolved in 0.05 cc. of isotonic solution of sodium chloride. The solid black represents generalized convulsive seizures; the lined portion represents lateral or focal seizures.

units of penicillin at intervals of at least eight hours. All injections were made through the same burr hole into the motor cortex. Six of the monkeys receiving 1,000 Oxford units had some form of convulsive seizure, 3 of which were generalized attacks. Six of those receiving 500 units had twitchings of the opposite extremities, whereas only 1 receiving 250 units had twitchings (fig. 1). It therefore seems that in most monkeys the local application of penicillin in doses of more than 500 Oxford units produced convulsive manifestations. The convulsive threshold has not been determined for the monkey, but from preliminary observations it is likely that it will be somewhat higher than in the monkey.

Electroencephalographic Manifestations.—If a cat or a monkey receives an injection of a solution of penicillin or if dry penicillin is placed under the arachnoid over the cerebral cortex while an electroencephalogram is being made, within ten minutes after the application spikes begin to appear in the leads about the area of application. These spikes are either uniphasic or biphasic and initially are present only in the leads from the area to which the penicillin has been applied. Within two or three minutes similar spikes are seen in leads taken from other portions of the cerebral cortex. These spikes occur every few seconds, and if the animal has not been curarized the spikes are usually accompanied by twitchings of one or both of the contralateral extremities. The spikes continue to occur at frequent intervals, gradually becoming closer together. After a series of spikes there is usually a period of decreased cortical activity. This series of spikes is the electroencephalographic manifestation of the myoclonic jerks of the extremities (local fit) (fig. 2). Usually they are seen within fifteen minutes after application of a convulsive dose of penicillin to the cerebral cortex. In twenty to thirty minutes after the application of penicillin the spikes become practically continuous in all leads for as long as five or six minutes. Such bursts are accompanied clinically by a generalized convulsive seizure.

The convulsion may stop suddenly, or its termination may be heralded by spikes occurring every two or three seconds. Electrical activity of the brain at the end of the seizure is almost abolished, the cortex appearing practically isoelectric. Within a minute small humps or rounded spikes begin to appear more prominently in the leads from the site of application of the penicillin. These spikes increase in frequency until the convulsive electroencephalographic pattern is fully developed again and the animal goes into another generalized convulsive seizure. This may take from three to four minutes, when the animal has a generalized convulsive seizure lasting three or four minutes.

When the entire sequence begins again. This electroencephalographic pattern has been followed for more than twelve hours (figs. 3 and 4).

FACTORS POSSIBLY INFLUENCING THE CONVULSIVE ACTIVITY OF PENICILLIN

Irritation as a Nonspecific Reaction to Injection.—That the convulsive effect might be due to a nonspecific reaction caused by injection of an irritating substance into the brain has been carefully investigated. In many cases 0.05 cc.

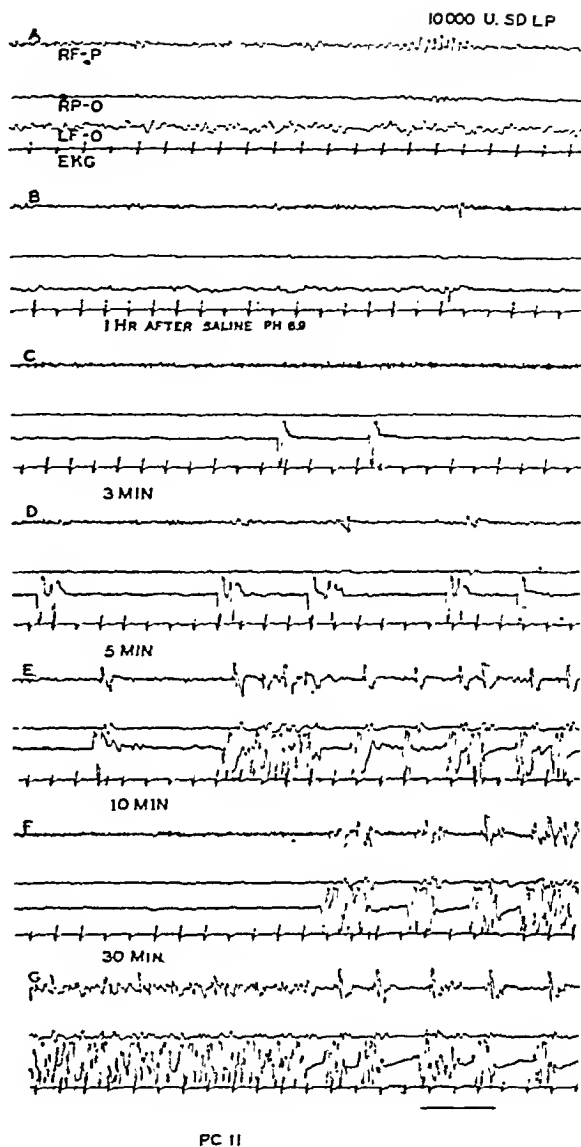


Fig. 2.—Electroencephalogram of a cat, which was prepared under vinethene and procaine hydrochloride anesthesia, curarized and artificially aerated, showing the effect of a subdural injection of 10,000 Oxford units of penicillin into the left parietal region. The leads were as follows: RF-P, right frontoparietal; RP-O, right parieto-occipital, and LF-O, left fronto-occipital; E.K.G., the two forelimbs. A, control record. B, one hour after subdural injection of 0.2 cc. of isotonic solution of sodium chloride adjusted to the pH of the penicillin solution. C, three minutes after subdural injection of 0.2 cc. of isotonic solution of sodium chloride at pH 7.3 containing 10,000 Oxford units of penicillin into the left parietal region. Spikes are present in the leads on the left side only. D, five minutes after the injection. The spikes are more frequent and beginning to appear on the right side. E, ten minutes after the injection. The spikes are present in all leads and occur in bursts of three to six. F and G, continuous record showing a short epileptic burst of activity. The line at the base of the records indicates an interval of one second.

of isotonic solution of sodium chloride has been injected into the cerebral cortex without deleterious effect. Even 0.05 cc. of 95 per cent alcohol caused no convulsive reaction when injected intracortically.

Concentration of the Drug.—The influence of concentration of the drug on the convulsive effects has been studied in several animals. Obviously wide ranges of concentration are impracticable, because of the small size of an animal's head. Within the concentrations used, 200,000 to 5,000 Oxford units per cubic centimeter, the amount of injected penicillin appears to be more important than its concentration in solution. If an initial dose of the drug does not cause convulsive manifestations, a subse-

was brought to a p_H of 7.3 by the addition of sodium hydroxide. Another solution of sodium chloride was made up with a p_H of 6.88; 0.1 cc. of this solution was injected into the cerebral cortex of a cat which had been prepared for electroencephalographic study. The electroencephalogram showed no changes within the next hour. Then 0.1 cc. of the isotonic solution containing 5,000 units of penicillin was injected into the cerebral cortex. Within ten minutes spikes began to appear and within ten minutes electrical phenomena characteristic of generalized seizures appeared. It seems, therefore, that the hydrogen ion concentration of the penicillin solution was not the factor responsible for the convulsive manifestations (fig. 2).

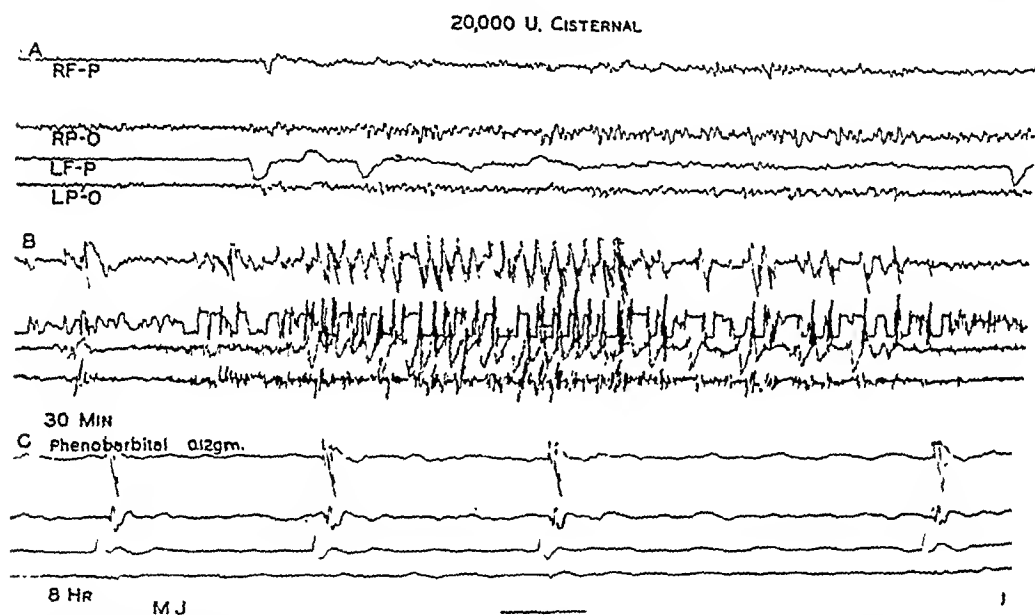


Fig. 3.—Electroencephalograms of a monkey (J), before (A) and after (B and C) the injection of 20,000 Oxford units of penicillin in 0.2 cc. of saline solution into the cisterna magna. Convulsive attacks occurred every two to five minutes for seven hours, being arrested by the intraperitoneal injection of 0.12 Gm. of phenobarbital sodium, although spikes still appeared in the electroencephalogram (C). The leads were as follows: RF, right frontoparietal; RP-O, right parieto-occipital; LF-P, left frontoparietal; LP-O, parieto-occipital. The horizontal line at the base indicates an interval of one second; the vertical line at the base to the right indicates a calibration of 60 microvolts.

quent larger injection of the same solution may produce fits. Moreover, highly concentrated injections in low doses have failed to induce epileptic phenomena in an animal which a day or two later promptly had seizures when larger doses of a less concentrated solution were injected intracerebrally.

Hydrogen Ion Concentration of the Penicillin Solution.—The possibility that the convulsive phenomena might be the result of the acidity or alkalinity of the solutions employed was readily tested. The p_H of the solution of sodium penicillin employed was found to be 6.88. It

Antibacterial Potency of the Penicillin Solution.—The possibility that the convulsant factor in commercial penicillin might be due to impurities and not associated with the antibacterial factor has been given serious consideration. Since we were unable to obtain pure crystalline penicillin, the problem resolved itself into an attempt to inactivate selectively one of the factors. Because more was known about inactivation of the antibacterial than of the convulsant factor, methods said to decrease the antibacterial potency were tested. Boiling the penicillin solution for thirty minutes, aging the solution for

enteen days, dissolving it in dehydrated alcohol and finally treating the penicillin solution with concentrated hydrochloric acid and then neutralizing it with sodium hydroxide were all tried.

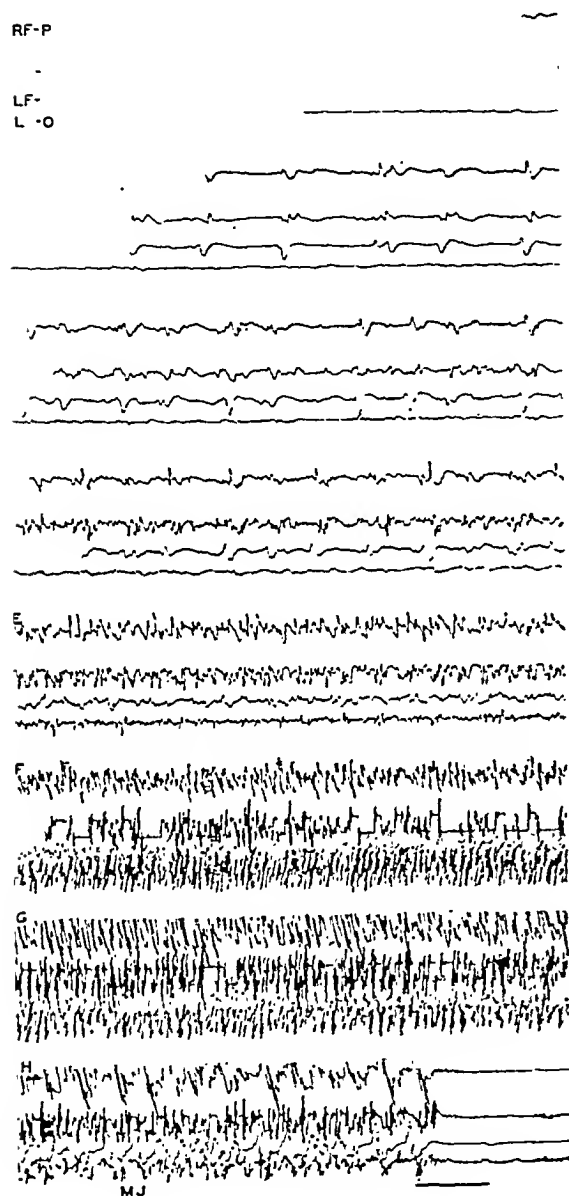


Fig. 4.—A series of electroencephalograms taken at one minute intervals from a monkey (J) approximately three hours after the injection of 20,000 Oxford units of penicillin into the cisterna magna. The leads are the same as in figure 3. The gradual development of the generalized fit is well demonstrated as well as the abrupt cessation of the seizure. Such convulsive manifestations recurred every two to five minutes and lasted five to eight minutes.

These methods decreased both the antibiotic and the convulsive effects about equally. Autoclaving the powder has not given consistent re-

sults, but in experiment it practically abolished the antibiotic factor but only slightly lowered the potency of the convulsive factor. This result indicates that the two effects may be separated but does not conclusively prove that the convulsive factor is not related to the antibiotic factor. When pure crystalline penicillin is available the question may be answered more conclusively.

Species Susceptibility.—The convulsive effect of penicillin on the central nervous system is dependent not only on the dose of the drug but also on the species of the experimental animals. As little as 20 Oxford units administered intracerebrally to mice may cause seizures, and ten times that amount may cause a fatal status epilepticus. For cats the threshold is probably about 1,000 to 2,000 Oxford units, and for monkeys, less than one half of that. Fortunately a considerably larger dose of penicillin may be injected intracerebrally or intraventricularly into human beings without producing convulsive manifestations. We have injected 5,000 Oxford units into the occipital cortex without causing clinical or electroencephalographic abnormalities. An injection of 20,000 Oxford units into the occipital cortex produced electroencephalographic changes but no clinical concomitant signs. Injected near the motor area, however, 10,000 Oxford units has given rise to twitchings of the face and hands for three hours. Since the full therapeutic effect of penicillin may be obtained with doses of 20,000 units or less, it seems improbable that the clinical advantages of this drug will be marred by its convulsive factor. This is particularly likely to be true since in practice the drug is injected not into normal cerebral cortex but into wounds or abscess cavities, the inflammatory linings of which impair diffusion of the penicillin to the adjoining nerve tissue. However, the amount of penicillin injected into the cisterna magna and the cerebral ventricles may well be limited by the convulsive factor.

SUMMARY

The application of commercial penicillin to the cerebral cortex of cats, dogs, monkeys and human beings has given rise to convulsive manifestations. The antibiotic and convulsive factors of penicillin appear to be closely related, for they are affected about equally by aging, boiling and acidifying the penicillin solution and by dissolving the penicillin in alcohol. In human beings penicillin applied to the cerebral cortex in doses of 10,000 to 20,000 Oxford units may produce convulsive manifestations.

MÉNIÈRE'S DISEASE IN A DEAF-MUTE

WALTER E. DANDY, M.D.

BALTIMORE

This report describes typical attacks of Ménière's disease during early life in a man who was congenitally deaf and dumb. It also contributes evidence concerning the underlying pathologic features of mutism.

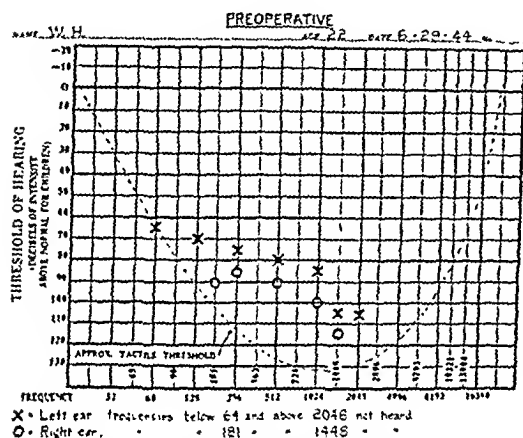


Fig. 1.—Audiogram of the patient (deaf-mute) taken before operation. The hearing for sounds interpreted only as noise is less on the affected side.

REPORT OF A CASE

W. H., a deaf-mute man aged 22, complained of izzy spells, associated with nausea and vomiting.

History.—So far as is known, the patient had never heard or spoken. He had scarlet fever at the age of 2 years but had no infection of the middle ear then or subsequently. His conversation was carried on through sign language; he heard nothing. He was bright and worked his way through high school and two years of junior college; during the latter period he played football.

Three months previous to the time of writing, attacks of rotary vertigo began and occurred with subsequent frequency. Every three or four weeks a severe attack ensued; during these, he became nauseated and frequently vomited; objects whirled. The attacks were heralded by a noise in the right ear (although he had no hearing). During the last attack he was bedfast for several days. During the attacks there was a sense of fulness about the right ear.

A test with the audiometer was interesting, in that certain wave frequencies were consistently registered as "noises," and the range of sounds was less on the affected side (fig. 1). That these were actual sound waves, though not appreciated as sound, was shown by

the fact that after total division of the right nerve all sounds were lost on that side (fig. 2) was then no appreciation of any wave: Bárány tests of vestibular function were not cause the Ménière attacks indicated the presence of vestibular function. The absence of disturbance following section of the nerve denoted the presence of this function on the opposite

Operation (June 29, 1944).—Total section of eighth nerve was done. After evacuation of terna magna, there was ample room, but beca rounded hillock of bone overlying the audit (fig. 3), the cisterna sulci lateralis and the nerve could not be reached safely. This mal has not been encountered heretofore in a serie cases. To gain access to the cerebellopontile was necessary to remove the outer cap of t bellum. This was never necessary in a serie vious cases and clearly demonstrated a cc abnormality in this region. The cisterna sulci was then easily reached and opened and the : nerve exposed. There was no porus acusticus usual anatomic type; the nerve passed into the bone directly and entirely filled the opening, wh

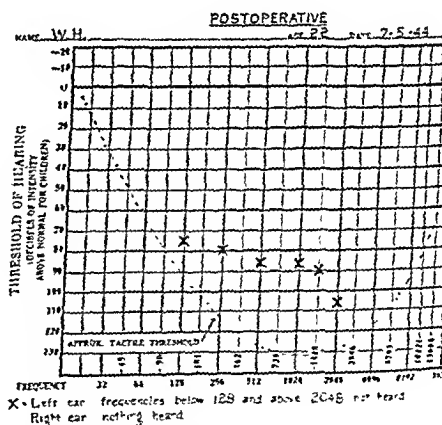


Fig. 2.—Audiogram of the same patient taken after operation. It shows complete loss of sounds interpreted as noise in the right ear following section of the right auditory nerve.

flush with the bone and dura, i. e., there was no bony opening about the nerve such as normally obtained at the acoustic foramen. Moreover, the nerve was much deeper than usual and was about 1.5 cm. from the bony hillock, which probably represented a greatly hypertrophied outer lip, which usually over

porus acusticus laterally. The eighth nerve was very small; I have never seen a smaller one. The seventh nerve, which is nearly always concealed beneath the auditory nerve, was in full view immediately anterior to it (fig. 3) and passed into the petrous bone with it in a normal relationship. The auditory nerve was then totally divided with the electrocautery. Because of its great depth, a piece of the nerve could be removed for microscopic study.

The patient made an uneventful recovery and left hospital eight days later. At the time of this writing, six months later, he had had no attacks and was working full time.

COMMENT

I know of no other reported case of Ménière's disease associated with congenital deaf-mutism.

An excellent contribution by Fraser (1931)¹ clearly demonstrates aplasia of the entire labyrinth with malformations of the labyrinth and the organ of Corti. Fraser's photographs of the end organs leave no doubt concerning the great defects of the end organs and therefore concerning the cause of deaf-mutism. He did not demonstrate or consider, and perhaps rightly so, a primary defect in the auditory nerve.

It has been my belief that Ménière's disease is always due to a lesion, congenital or acquired, in the auditory nerve itself and not in one of the end organs.² If Ménière's disease is not more common in deaf-mutes than in the general population, Fraser's demonstration of a primary con-

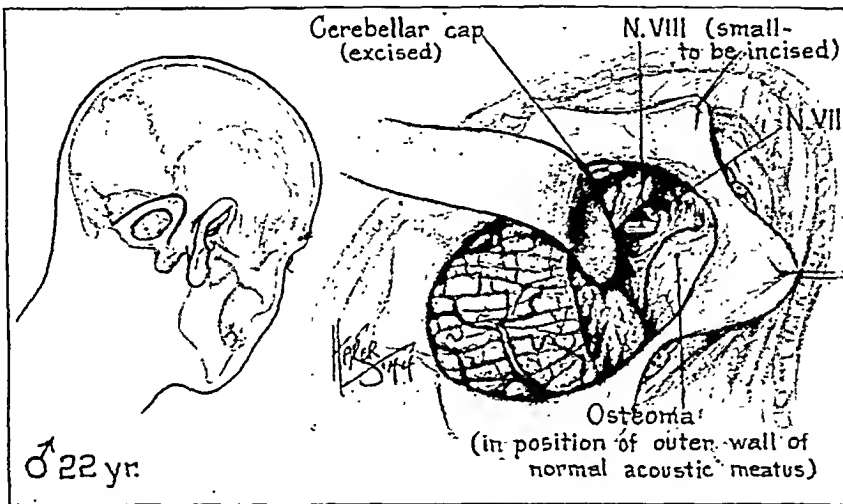


Fig. 3.—Operative sketch showing congenital malformations in the patient: (1) the large hillock of bone which corresponds in position with the outer lip of the normal acoustic foramen and which necessitated resection of the cerebellar cap in order to expose the eighth nerve; (2) the deeply placed eighth nerve, which entered the bone directly and not through a concavity, such as obtains with a normal porus acusticus; it was well below the hillock of bone; (3) an extremely small auditory nerve; (4) the exposed seventh nerve which is normally obscured by the auditory nerve.

This rarity may be seeming or real. Ménière's disease is not too well recognized, but in two great centers for teaching the deaf and dumb—the great Goldstein school in St. Louis and the school in Cleveland headed by Dr. Kinney—I have made inquiry and have been advised that a case of this disease has never been observed in either of these centers. Its existence would undoubtedly be recognized in these institutes, for both have been controlled by highly competent otologists. There is therefore no reason to believe that Ménière's disease is more frequent among deaf-mutes than in the general population and therefore that the inherited deafness is contributory to the development of this disease. Little is known concerning the underlying pathologic condition of deafness and dumb-

genital defect of the end organ would be in consonance with the view that a defect in the end organ does not lend itself to subsequent development of Ménière's disease. It is possible that there may be a second and a rare cause of this syndrome, i. e. a primary congenital neural defect of which there was evidence in the case here reported. This may or may not be in addition to a congenital defect in the labyrinth. It is difficult to believe that the findings in this case were more than an unusual coincidence; i. e. probably the primary cause of the mutism

1. Fraser, J. S.: The Pathology of Deaf-Mutism. *Proc. Roy. Soc. Med.* 25:861, 1932.

2. Dandy, W. E.: Certain Functions of the Roots and Ganglia of the Cranial Sensory Nerves. *Arch. Neurol. & Psychiat.* 27:22 (Jan.) 1932.

was in the labyrinth and not the defective auditory nerve. Should the incidence of Ménière's disease in deaf and dumb persons later be shown to be higher than that in the general population, a second type of mutism might then be considered, i. e. one due to a primary defect.

The old French theory that mutism was due to a primary cerebral malformation is no longer tenable, at least in more than a small percentage of cases. Goldstein³ has demonstrated unequivocally that the lesion is peripheral, because, with

few exceptions, speech can be developed in deaf-mute if treatment is instituted early. This has been substantiated by others. Goldstein and Kinney⁵ have demonstrated that in some cases there are "islands of sound perception" which, however, are beyond the limits of practical utilization. These and total loss of hearing after section of the auditory nerve are well illustrated in the case here reported.

4. Goldstein, M. A.: *Problems of the Deaf*, St. Louis, Laryngoscope Press, 1933.

5. Kinney, C. E.: *Interpretation of Hearing in Deafness*, St. Louis, Laryngoscope Press, 1943.

3. Goldstein, M. A.: *The Acoustic Method for the Training of the Deaf and Hard-of-Hearing Child*, St. Louis, Laryngoscope Press, 1939.

SYNDROME OF TRAUMA TO THE PSOAS MUSCLE

MAJOR ELLIOTT MICHELSON

MEDICAL CORPS, ARMY OF THE UNITED STATES

The psoas muscle is a long, powerful muscle which, in spite of its virtual continuous activity when a person is sitting and walking, is never subject to direct violence and is rarely indirectly traumatized. Strandell¹ recently reviewed the literature and cited 13 cases of subcutaneous rupture of the iliopsoas muscle, in 8 of which the rupture occurred in a normal muscle. Haldeman and Soto-Hall² reported 2 cases of trauma to the psoas muscle in a series of 104 injuries to muscles and tendons. Trauma to the psoas muscle may produce fibrillar, partial or complete rupture of the muscle bundles. The clinical picture depends on the degree of rupture, the site and size of the secondary hemorrhage, the irritation of contiguous nerves and structures and such complications as formation of a cyst, calcification and infection. Strandell has shown that a definite diagnostic picture is obtained, consisting of sudden acute pain, which is often accompanied by a knocking sound, followed by a latent symptomatic period, with pain and disability returning within an hour to several days. A case of trauma to the psoas muscle is here reported, because it too reveals this interesting clinical syndrome. A hitherto unmentioned diagnostic sign, deviation of the lower pole of the kidney and the upper third of the ureter by the mass of the psoas muscle, is described.

Knowledge of the anatomy of the region containing the psoas muscle is invaluable in understanding this clinical entity. The psoas muscle takes its origin from the lateral border of the vertebral bodies of the twelfth dorsal and the upper four lumbar vertebrae together with the intervening disks and the transverse processes of the lumbar vertebrae. The muscle unites with the broad iliac muscle, which takes its origin from the inner aspect of the ilium, and together they slide beneath the inguinal ligament as a tendon to insert into the lesser trochanter. The muscle flexes, adducts and externally rotates the

femur, and if the femur is fixed the spine and pelvis are flexed. The muscle is covered by a broad, firm fascial sheath, which is attached mesially to the anterolateral border of the lumbar vertebrae and laterally to the anterior layer of the lumbodorsal fascia. Superiorly the fascia opens directly into the posterior mediastinum, and inferiorly it gives rise to a bursa, which is situated on the anterior aspect of the hip joint and may communicate with the joint proper. The sheath is covered by areolar tissue, which serves as a bed for the kidney, ureter, ascending colon, duodenum and root of the mesentery on the right and the kidney, ureter and descending colon on the left. The blood supply of the psoas muscle comes from the ilio-lumbar branch of the hypogastric artery, the deep circumflex iliac branch of the external iliac artery and the lumbar branches of the aorta. There are numerous small lymph glands in the vertebral insertions of the psoas muscle fibers, and a large chain of lymph channels, which drain the lower extremities and the pelvis, lies above the sheath of the psoas muscle. The twelfth dorsal nerve emerges through the diaphragm and passes behind the psoas muscle. The iliohypogastric nerve runs through the psoas muscle just below the renal vessels; the ilioinguinal and lateral femoral cutaneous nerves travel beneath the psoas muscle, and the genitofemoral nerve runs first through the psoas muscle at the level of the second lumbar vertebra and then along its anterior sheath. The femoral nerve lies inside the muscle from its origin in the plexus down through the lacuna musculorum.

In view of the intimate association between the lymph glands and the vessels draining the pelvis and the lower extremities, it is easily understood how infection of the lower extremities might drain into the lymph chain of the psoas muscle, with suppurative adenitis and formation of an abscess within the psoas muscle. Infection along the root of the mesentery, perforation of the bowel, diverticulitis or appendicitis by agglutination with the anterior sheath of the psoas muscle may also produce abscesses of the psoas muscle. Tuberculosis of the dorsal and, in rare

1. Strandell, G.: Subcutaneous Rupture of the Iliopsoas Muscle, *Acta chir. Scandinav.* 86:149, 1942.

2. Haldeman, K. O., and Soto-Hall, R.: Injuries to Muscles and Tendons, *J. A. M. A.* 104:2319 (June 29) 1935.

instances,³ of the cervical vertebrae may dissect down through the posterior portion of the mediastinum and enter directly into the psoas muscle. Inflammation of the psoas muscle produces contracture with flexion, adduction and external rotation of the femur. By pulling on the intervertebral disks and the transverse processes on that side scoliosis is produced, with evident concavity toward the affected side. In view of the fact that the psoas muscle lies in an oblique position to the vertebrae, any expansion of the muscle from infection or tumor will push structures lying above it lateralward into the lumbar fossa. Retrograde pyelograms therefore should and do reveal displacement of the lower pole of the kidney and the upper third of the ureter when a mass in the psoas muscle is present. Sudden increase in pressure within the psoas sheath due to hemorrhage and/or infection may irritate the enveloped nerves sufficiently to produce symptoms of neuritis. Nerves are not involved with chronic slowly progressive lesions, such as arthritis of the spine due to tuberculosis. Acute and chronic masses of the psoas muscle may present in the flank, the abdomen, the pelvis or the inguinal position. Pus within the sheath dulls or obliterates the outline of the psoas muscle on the roentgenogram. In hemorrhage, with an intact psoas sheath, the outline of the muscle will be preserved on roentgenograms of the kidney, ureter and bladder and at times bulging of the lateral border of the muscle may be noted.

The following case report typifies the syndrome and introduces a pathognomonic roentgenographic sign.

REPORT OF A CASE

A 19 year old soldier, identical twin, with no past record or familial history of bleeding, was well until twelve days prior to his admission to the hospital, when he executed a jackknife dive from a 12 foot (3.6 meter) board, twisted his body to the left in midair and felt a sudden tearing pain in the right lumbar region. The pain disappeared and did not prevent him from swimming about and later from performing his normal duties, which included long marches. Several days later he noticed dull aching pain in the right side of his back, and in the week prior to his admission to the hospital the pain became more severe and constant. The pain was increased on walking and deep breathing and was not relieved by change in position. A sensation of soreness in the scrotum was noted for approximately one week, and the patient felt as if he had been kicked in that area. The urine was said to have been slightly red several days prior to hospitalization, but it was otherwise normal. When he walked about he felt as if his right leg was weaker and shorter than his left. There were no urinary or digestive symptoms. He had felt warm for several days, and the night before hospitalization he had noted a slight chill.

3. Alpert, L.: Report of a Case of Psoas Abscess Resulting from Tuberculosis of the Cervical Spine, *New England J. Med.* 211:675, 1934.

On admission to the hospital the soldier appeared to be moderately ill and in severe pain. He assumed a supine position, turning slightly to the left with right knee and thigh moderately flexed. On examination fullness in the right flank was noted, with severe spasm and prominence of the lateral costal interdigitations of the right latissimus dorsi muscle. The tenderness in the right costovertebral angle was exquisite, could be followed forward to the flank. There was extreme scoliosis of the lumbar spines to the left, with concavity toward the right. An apparent but not actual shortening of 1 inch (2.5 cm.) of the right leg was noted. No tenderness was evident over the vertebral spines and the paravertebral muscles. The abdomen was flat, with slight tenderness on deep pressure in the right upper quadrant. Slight hyperesthesia was displayed in the right groin along the course of the ilioinguinal nerve, with subjective soreness over the scrotal skin. Ludloff's sign (to be discussed later in the paper) was positive. The reflexes were normal.



Fig. 1.—Pyelogram showing a normal pelvis and calices and definite lateral deviation of the upper third of the right ureter and the lower pole of the right kidney.

The temperature was 101 F., the pulse rate 100, the respiratory rate 20. The red blood cell count was 4,600,000, with a hemoglobin content of 80 per cent; the white cell count was 11,000, with 73 per cent polymorphonuclear cells. A roentgenogram of the abdomen revealed normal shadows of the psoas muscle and vertebrae. Repeated examinations of the urine gave negative results for albumin, casts and cells. Cyst examination showed a normal bladder with normal renal function and obstruction of the right ureter. Retrograde pyelogram (fig. 1) revealed a normal pelvis and calices and definite lateral deviation of the upper third of the right ureter and the lower pole of the right kidney.

The diagnosis of a mass in the right psoas muscle which was pushing the kidney and ureter laterally into the lumbar fossa, was thus established. In view of the history of acute trauma the mass was thought to be an infected hematoma. The patient was given sulfathiazole but continued to have a remittent fever with a temperature which hovered about 101 F. and complained of a great deal of pain in the right

the back and in the right thigh, and the scoliosis the flexion contracture of the right thigh increased. A few days after his admission to the hospital operation was performed and an infected hematoma of the right psoas muscle drained through a modified Faxon⁴ incision. This incision, rather than the classic exploratory incision, was used because extension of the suppurative process into the subphrenic space was anticipated. With the patient under spinal anesthesia induced with tetracaine hydrochloride an oblique incision was made in the right posterior axillary line over the twelfth rib, and the distal 3 cm. of the rib was resected. The muscles were split at the level of the first lumbar vertebra, the peritoneum together with Gerota's fascia was pushed forward and the psoas muscle was found to be covered by a dull gray edematous fascia. Incision through the sheath revealed a large cavity containing pus and blood. The cavity measured 10 cm. in

COMMENT

Injuries of the psoas muscle are rare, and Strandell's report of 13 cases contained only 8 authentic cases of rupture of a normal muscle. All these 8 cases involved young men; 3 of the ruptures occurred while the men were lifting heavy weights; 2 occurred when the men fell backward; 1 happened while the man was in a split position and 2 occurred while the men were jumping over a fence or somersaulting over a box. The case reported here can be likened to the last in that the soldier incurred his injury while twisting his body in a jackknife dive.

The typical clinical picture in these cases is sudden intense pain in the lower portion of the abdomen, in the flank or in the hip, often accompanied by a knocking sound, which is said to be characteristic of rupture of a tendon. The pain disappears quickly as a rule, and the patient is able to work for hours or days before the pain returns. The victim begins to walk with a limp and notes difficulty in raising the affected leg. In this case the soldier felt that his right leg was shorter than his left.

Ludloff's sign¹ is said to be positive in all cases of severe irritation and rupture of the psoas muscle, and it was positive in this case. The sign is positive when the patient can flex the thigh while in the recumbent position but is unable to lift the thigh while in a sitting position with the hips flexed at 90 degrees. The test depends on the flexion activity of the rectus femoris and the tensor fascia lata muscle without aid of the psoas muscle with the patient in the supine position. When these muscles are relaxed with the patient in the sitting position disability of the psoas muscle prevents flexion or lifting of the thigh. In this case the sign was positive before and negative after operation. The hip joint is free with passive motion at first, but later flexion contracture and pain prevent mobility of the joint.

A distinct mass is usually felt below the inguinal ligament, although at times fullness alone may be noted in the abdomen, the iliac fossa or the lumbar region.

Neural lesions have been reported in association with trauma to the psoas muscle; in 1 case there was involvement of the femoral nerve with paralysis of the quadriceps femoris and adductor muscles and loss of sensory function of the lateral femoral and the saphenous nerve. In the case reported here there was temporary sensory im-



Fig. 2.—Pyelogram taken six weeks after the operation, showing normal shadows of the psoas muscle with no evidence of lateral deviation of either the ureter or the kidney.

length and 5 cm. in diameter and was situated at the level of the first, second and third lumbar vertebrae. There was no extension of the inflammation to the subphrenic or the periphrenic space. A large Penrose drain was inserted into the cavity, and the wound was closed in layers about the skin. Cultures of pus revealed *Staphylococcus aureus nonhaemolyticus*. The temperature gradually returned to normal. The drains were slowly removed, and the drainage disappeared in seven days. Six weeks after the operation, cystoscopy showed a normal bladder and renal function, and retrograde pyelograms revealed normal shadows of the psoas muscle with no evidence of lateral deviation of either the ureter or the kidney (fig. 2). Ludloff's sign was negative postoperatively. The patient was discharged to full military duty, and a follow-up letter six months later reported the soldier to be completely well and on active military duty.

4. Faxon, N.: Logical Approach to Subphrenic Abscess, *Am. J. Surg.* 54:114, 1941.

pairment of the ilioinguinal nerve. Tallroth⁵ said that 5 cases of hemophilia associated with spontaneous hemorrhage in the iliopsoas muscle have been reported in the literature. He described a sixth case in which there was also temporary paralysis of the femoral nerve. The prognosis is usually good for both motor and sensory paralysis of nerves as long as operation with decompression of the intramuscular pressure is performed early.

In the reported cases the psoas muscle was poorly visualized or obliterated when the sheath was torn and blood diffused beyond the confines of the muscle. Bulging of the lateral border of the psoas muscle was noted in 1 case. Deviation of the ureter and kidney by a mass in the psoas muscle has been noted, but no emphasis has been placed on its diagnostic importance. McNally and Case⁶ reported on an echinococcus cyst of the psoas muscle which produced definite lateral deviation of the upper urinary tract. Beer's⁷ report described ureteral deviation in 2 cases of abscess of the psoas muscle which were first thought to be cases of perinephritic abscess.

Extravasated blood in muscle tissue may become absorbed, produce loculated cysts, calcify or become infected. Beer⁷ mentioned a case of abscess of the psoas muscle with a loculated calcific mass which might have been due to previous injury. If infection supervenes by vascular or lymphatic extension, chills and fever appear. This usually occurs, according to Racz,⁸ in seven to eight days after the acute injury. With the onset of suppuration there is an increase in pain with radiation down the thigh, and the patient appears extremely ill. The infection may become localized or may spread downward toward the lesser trochanter. If the iliac bursa is involved, signs resembling coxitis with severe pain on motion of the hip joint may be noted. In a small percentage of cases in which the iliac bursa communicates with the hip joint secondary synovitis will occur. The suppurative process may break through the fascia at the lesser trochanter and present beneath the inguinal ligament as a subcutaneous abscess. The abscess may penetrate the anterior sheath of the psoas muscle, giving rise to peritoneal irritation, paralytic ileus and clinical signs of an intra-abdominal mass.

It is possible for the abscess to invade fascia with formation of a perinephritic to perforate the peritoneum with con peritonitis and in rare instances even to into contiguous bowel.⁹ Infection occurs 25 per cent of Strandell's cases, with no fatality. Two of the 5 patients with hemophilia reported on by Tallroth became infected, and 1 died.

Differentiation of abscess of the psoas from other disease may at times be difficult in those cases in which there is a mass in the muscle with no history of acute injury or constitutional symptoms of acute suppurative process. Possibility of arthritis of the spine due to tuberculous infection should be considered. The Mantoux and roentgenograms will usually reveal the logical factor. Osteomyelitis of the femur usually starts clinically with contracture of the psoas muscle, and careful examination will usually reveal local tenderness; roentgenograms will reveal normal shadows of the psoas muscle and of the part of the urinary tract. So-called pyomyositis⁹ occurring in young children from fungous infection or by lymphatic extension from infection of the skin or bones of the lower extremities produce the typical syndrome of trauma to the psoas muscle. In this syndrome the onset is acute, no previous traumatic episode is noted on examination reveals pronounced flexor contraction, occasional neuralgic symptoms and a positive Ludloff sign. Roentgenograms will show normal shadows of the psoas muscle, but if suppuration ensues the obturator muscle (bulging of the medial outline) will be present. Perinephritis may give a similar history and signs, but roentgenograms will usually reveal obliteration of the psoas muscle and normal position of the ureter and kidney. Perforation of appendix,¹⁰ sigmoid diverticulitis¹¹ and perforation of the ileum by a foreign body¹² have been reported as the cause of abscess of the psoas muscle, and these possibilities should be entertained. Subphrenic abscess may simulate suppuration in the psoas muscle, but careful roentgenographic and fluoroscopic examination of the diaphragm should locate the lesion.

There are no doubt numerous minor degrees of trauma to the psoas muscle which may produce

5. Tallroth, A.: Hemophilia with Spontaneous Hemorrhage in the Iliopsoas Muscle Followed by Injury to the Femoral Nerve, *Acta chir. Scandinav.* 82:1, 1939.

6. McNally, A., and Case, J. B.: Echinococcus Cyst of the Left Psoas Muscle, *Am. J. Surg.* 51:419, 1941.

7. Beer, E.: Psoas Muscle Abscess Simulating Perinephritic Abscess, *J. Mt. Sinai Hosp.* 4:928, 1938.

8. Racz, B.: Acute Psoas Abscess Arising in Sports, *Zentralbl. f. Chir.* 64:452, 1937.

9. Schroeder, E.: Primary Pyomyositis, *Acta chir. Scandinav.* 81:138, 1938. Cohen-Solal, L.: Acute Pyomyositis, *Suppurations Developing in the Sheath of the Iliopsoas*, *Rev. de chir., Paris* 74:534, 1936; abstracted, *Surg. Gynec. & Obst.* 64:162, 1937.

10. McCorkle, H., and Stevenson, J.: Psoas Abscess of the Appendix, *Surgery* 3:547, 1938.

11. Lyall, A.: Acute Psoas Abscess Caused by Diverticulitis, *Brit. J. Surg.* 24:192, 1936.

12. Sinclair, A. S.: A Case of Psoas Abscess Due to Osteomyelitis of the Spine But to Foreign Body, *Canad. M. A. J.* 45:157, 1941.

ld pain in the back and contiguous intestinal itation. The cause in some cases of meralgia resthetica may be subcutaneous injury of the as muscle. Pain in the back associated with esthesia along the saphenous, lateral femoral taneous and genitofemoral nerves should sug- st injury of the psoas muscle. Mild fibrillar jury of the psoas muscle should be treated nservatively with rest and local heat. In those ses in which there are associated mild vaso- tor changes and no involvement of peripheral as the treatment is expectant, but if signs neuritis or infection supervene operation is icated. For all large hematomas in the ab- of a blood dyscrasia, incision and drainage ould be practiced. The incision depends on e site of the mass in the psoas muscle. In the ac fossa the best surgical approach is the longi- dinal incision of Ludloff; one searches for the scess on the medial aspect of the thigh between e gracilis and the adductor longus muscle, ing through the pectineus muscle, and should cate it either within or without the iliopsoas uscle.¹³ In masses above Poupart's ligament, Gibson extraperitoneal incision for explora- on of the lower ureteral region is excellent. In asses in the upper portion of the psoas muscle e approach may be made through the usual har renal exploratory incision or a modifica- on of Faxon's posterior subphrenic incision.

13. Freiberg, J. A., and Perlman, R.: Pelvic Abscesses ssociated with Acute Purulent Infection of the Hip int, *J. Bone & Joint Surg.* 18:417, 1936.

SUMMARY

A patient with an infected hematoma of the psoas muscle presented the typical clinical syn- drome associated with trauma to the psoas muscle.

With this syndrome a history of sudden pain associated with violent exercise followed by a latent asymptomatic period and subsequent pain and disability is obtained. Examination reveals flexion contracture of the thigh with adduction and external rotation. There are scoliosis of the lumbar vertebrae away from the affected side and apparent shortening of the leg on the affected side. A mass or fulness is found in the flank, abdomen, iliac fossa or inguinal region. A normal outline of the psoas muscle is seen on roentgenograms, and lateral deviation of the upper third of the ureter and the lower pole of the kidney on retrograde pyelography is noted. Irritation of nerves is found in acute large hemor- rhagic extravasations, with complete recovery following adequate drainage. Complications of hemorrhage in the psoas muscle include forma- tion of cysts, calcification and infection. Occa- sionally abscesses of the psoas muscle may perforate into perinephric and peritoneal spaces and contiguous bowel. If the abscess descends to the level of the lesser trochanter, bursitis, synovitis or subcutaneous abscess may result. The syndrome should be differentiated from perinephritis, coxitis, osteomyelitis of a vertebra or of the femur, primary psoitis and intra- abdominal abscess. Early operation results in recovery and no permanent disability.

EXPERIENCE WITH CALCULUS OF THE BLADDER IN NORTH CHINA

PHILIP B. PRICE, M.D.

SALT LAKE CITY

Calculus of the bladder is endemic in parts of China. Thomson¹ reported 2,949 lithotomies performed at the Canton Hospital between the years 1861 and 1919. Olpp and Kuhne,² in the same province observed 189 cases of vesical calculus in nine years. Cochran³ in Anhwei Province, in Central China, treated 227 patients with calculus of the bladder in the course of twelve years. In five years I saw about 150 patients with vesical calculus at the University Hospital in Tsinan, capital of Shantung Province; 126 of these patients admitted for treatment form the basis of this report.

Shantung is a northern coastal province. The dense population, estimated at about 38,000,000, is largely rural, wresting a subsistence from the arid soil by means of a primitive system of irrigation. Although the winters are long, the total number of hours of sunshine during the year is large.

INCIDENCE

Three fourths of the patients with vesical calculus came directly from the country; the remainder gave city or town addresses, but the latter group included several boys of farmer stock who were attending school in the city. All of the patients, without exception I believe, belonged to the poorer classes of society; 4 were beggars.

In the present series, 121 patients were males and 5 were females.

The age incidence was remarkable. Seventy-four per cent of the patients were between 5 and 15 years and only 7 per cent over 25 years of age. In 35 per cent of the series urinary symptoms began during the first three years of

life, and in 72 per cent the onset of symptoms was before the age of 7 years.

Symptoms frequently started in the spring exacerbations of symptoms were most common in the spring months and least common in the summer.

ETIOLOGY

Infravesical obstruction was found in 10 per cent of the patients. Three patients had stones which had formed around a foreign body in the bladder. There was no evidence in the history, physical examination or analysis of the vesical calculi that renal stone had occurred in any of these patients or that it had played part in the pathogenesis of the disease. In the series renal stone was rarely observed in that province.

Shantung is a dry region with extremes of temperature. The water is extremely hard. It is noteworthy that the patients were most numerous in the hot summer months, when consumption of water is large but when the urine is likely to be concentrated.

The seasonal incidence of symptoms suggests a dietary factor in the pathogenesis. During the long winters the people, if poor, subsist chiefly on cereals, vegetable oils and vegetables poor in color. Children are commonly weaned after the second or third winter, and during the next three or four years they are fed largely on cereal especially in winter. Although in summer there is a larger variety of foods available, even in the poor, evidences of vitamin deficiency are found commonly in patients of all ages, but especially in children. Some of my patients with vesical stone complained of night blindness. Furthermore, many of the little country children run naked, or nearly naked, in the bright sunshine during the warm months of the year. It is probable, therefore, that hypervitaminosis D and vitamin A deficiency coexisted in many instances, a combination which has been used to produce urinary calculi experimentally in animals.⁴

From the Department of Surgery, University of Utah School of Medicine.

1. Thomson, J. O.: *Lithiasis at the Canton Hospital, China M. J.* 35:347, 1921.

2. Olpp and Kuhne, cited by Jefferys, W. H., and Maxwell, J. L.: *Diseases of China, Including Formosa and Korea*, Philadelphia, T. Blakiston's Son & Co., 1910, pp. 540-586.

3. Cochran, S.: *Choice of Operation in Vesical Calculus, China M. J.* 27:285, 1913.

4. Best, C. H., and Taylor, N. B.: *The Physiological Basis of Medical Practice*, Baltimore, Williams & Wilkins Company, 1943, p. 1211.

SYMPTOMS

Most of the patients had a far advanced condition, having been brought to the hospital as a last resort. The duration of symptoms ranged from five days to thirty years, the average being three years. A history of attacks with symptomatic intermissions was characteristic. The following incidence of symptoms was noted:

Symptom	Percentage
in	96
Benign	86
Suprapubic	28
Perineal	17
Lumbar	7
Rectal	1
Referred to thighs.....	1
Difficulty in micturition.....	91
Frequency	76
Sticking on penis for relief of pain.....	64
Hematuria	45
Urine expressed drop by drop.....	42
Stoppage of urine.....	40
Straining on head and shaking body for relief of stoppage or of pain.....	38
"Halky" urine	25
Protrusion of anus or prolapse of rectum.....	21
Passage of small stones or sand.....	16
Incontinence of urine.....	15
Acute retention of urine.....	5

DIAGNOSIS

In an advanced stage the symptoms were so typical that the diagnosis was rarely in doubt.

In 30 per cent of patients the stone or stones could be felt through the rectum. The ability to do so usually indicated a large stone fixed in position by a contracted bladder, by adhesion to the bladder wall or by impaction in the prostatic portion of the urethra.

Roentgenographic examination rarely failed to provide reliable and accurate information regarding the number, size, position and even structure of the stones. Two patients had stones which cast no shadows, and 1 patient (not in the present series) who had urethral obstruction and roentgenographic signs of vesical stone was found at operation to have a greatly thickened, contracted bladder filled with chalky urine, but no stone. Multiple calculi were not uncommon, but the usual finding was a single large calculus. The largest stone encountered was hourglass in shape and 9 cm. long and weighed 235 Gm. The patient had had symptoms for thirty years.

Cystoscopic examination was not employed routinely. Since most of the patients were small children and poor surgical risks, it did not seem wise to subject them unnecessarily to the additional administration of an anesthetic and the trauma of a cystoscopic examination. Even in adults it was often impossible to carry out satis-

factory cystoscopic examinations because of severe cystitis, contracted bladder or stones impacted in the urethra.

Two patients had obstructive phimosis; 1 had a traumatic stricture of the membranous urethra and 2 had strictures following gonorrhea. There were no cases of prostatic enlargement or obstruction.

Some degree of cystitis was almost always present; many patients had gross infection. Usually, on the patients' admission to the hospital, the bladder was irritable and spastic and would tolerate only a small quantity of urine or instilled fluid, but great improvement usually resulted after a few days of simple drainage and gentle irrigations. Some bladders were contracted and fibrosed, however, and improved only slightly during the preoperative regimen.

More than half the patients on hospitalization showed serious impairment of renal function, as measured by excretion of phenolsulfonphthalein; however, many of these patients improved remarkably during the preoperative period. The patients with the most severe involvement had tenderness in the costovertebral angles and an increase in the nonprotein nitrogen of the blood, and they excreted only traces of phenolsulfonphthalein in two hours.

Many of the patients were malnourished. Anemia and hypoproteinemia were frequently observed. Intestinal parasites were present in almost every case. Protrusion of the anal mucosa or true prolapse of the rectum from excessive straining was not uncommon in the younger children. A minor, but annoying, complication was dermatitis, due to incontinence of urine.

PREOPERATIVE TREATMENT

Because of the poor physical condition of many of the patients, emphasis was laid on unhurried, adequate preoperative care. Rest in bed, sedation, use of an indwelling urethral catheter, gentle irrigations and instillations, administration of urinary antiseptics by mouth, institution of a high caloric diet, treatment of anemia and intestinal parasites, correction of fluid and electrolytic balances and general nursing care seldom failed to bring about pronounced general improvement. Especially important was employment of the indwelling catheter; if properly placed, it usually relieved the pain and spasm to a large extent and provided for the all-important free drainage of urine.

Two patients with tightly impacted stones and acute retention required suprapubic aspiration of urine; 2 others required preliminary suprapubic cystostomy. It was found advisable to place the

latter patients prone on a Bradford frame, so that the urine would drain freely, dripping into a pan.

SUPRAPUBIC LITHOTOMY

The procedure to be described was evolved at the University Hospital during a period of several years.

Operative Technic.—Immediately before operation, preferably before induction of the anesthesia is started, a relatively large soft rubber catheter is introduced through the urethra and the bladder is irrigated repeatedly with isotonic solution of sodium chloride or a solution of boric acid until the fluid returns clear. No force other than gravity is used in the irrigation, the fluid being poured into the barrel of a large glass syringe, the nozzle of which is connected directly to the protruding end of the catheter. The capacity of the bladder under such conditions is noted; frequently it is not more than 50 or 75 cc. when this small amount of pressure is used. After the irrigation, the piston of the syringe is engaged, and a corresponding amount of air is injected slowly into the empty bladder. The catheter, pinched with a clamp, is left in place. This gentle irrigation and measured inflation obviate all danger of rupture of an ulcerated bladder wall or of air embolism; it will not even cause bleeding of congested mucosa.

The suprapubic region is cleaned and draped. A vertical midline incision is made about twice the length of the smallest diameter of the stone, as seen on the roentgenogram. The pyramidalis muscle, which may be greatly hypertrophied, is best split in the midline from below upward. Care is taken not to bare the pubic bone. The anterior surface of the bladder is disturbed as little as possible, the peritoneal reflection being rubbed upward gently with gauze in the midline only. Nicking or tearing the peritoneum at this stage is of no consequence provided the defect is observed and is closed promptly and completely. It is not necessary to discontinue the operation on that account.

The presenting wall of the bladder is held forward with two traction sutures of medium silk, which pass through all the coats of the viscus. This maneuver not only prevents the surgeon from losing his way while dissecting through the sometimes thick fibrous bladder wall but keeps the mucosa from retracting and thus facilitates subsequent closure. The circulating nurse then reaches a hand under the drapes and removes the clamp from the catheter, so that any fluid inadvertently left in the bladder may have an opportunity to escape. The bladder wall is incised vertically, the two large midline veins being avoided if possible. This incision, which is about one and a half times the diameter of the stone, is first carried to but not through the mucous membrane, so that full hemostasis may be secured before the vesical cavity is opened. This is an important point, for blood in the bladder may ruin all chances of a smooth postoperative course. A nick in the mucosa permits air in the bladder to escape harmlessly, but should any fluid appear the opening is promptly closed by crossing the traction sutures until the fluid is aspirated by means of a syringe, with a long blunt nozzle thrust through the hole in the mucosa. The escape of any of this infected fluid into the incision is to be avoided, since it results almost inevitably in postoperative infection and leakage of urine. The mucous membrane is now opened widely, exposing the stone in the base of the bladder.

At this point the surgeon inserts his finger cautiously into the bladder. If the stone is adherent to the wall

of the bladder, it must be freed gently. The stone is brought forward on the finger and is rotated, it may be grasped across its shortest diameter with an appropriate forceps introduced alongside the finger, forceps and stone are removed, particular being taken not to contaminate the wound. In the case of a large stone it is well to protect the wound with dry gauze. The finger is now introduced and the entire vesical cavity is palpated systematically for other stones, diverticula, incrustations, or other abnormalities. If none is found, the circulating nurse again reaches under the drapes and pulls the catheter until the internal end lies in proper position protruding about an inch (2.5 cm.) into the bladder. Thereupon the palpating finger is withdrawn, thus contaminating the wound, and the surgeon draws on his gloves. The bladder should not be irrigated during operation, since nothing of value is accomplished thereby, but much harm may be done by infecting the incision.

The bladder wall is usually closed without drain in three layers. First, the mucosa is repaired with a continuous suture of 000 plain surgical gut, much of the peritoneum is closed after a McBurney incision. The next step, which is contrary to the usual teaching adopted because it restores normal anatomic relations, reduces to a minimum the defect as seen from the bladder, prevents bleeding into the bladder, lessens the chances of postoperative leakage of urine. Next, the muscular (or fibrous) walls are approximated accurately without invagination with several interrupted sutures of 00 or 0 chromic surgical gut. Finally, loose areolar tissue on the anterior surface of the bladder is drawn over the defect with a continuous suture of fine plain surgical gut. The abdominal wall is closed with a small rubber drain being left in the space of Retzius. To insure immobility, the catheter is anchored to the skin with sutures in the prepucial fold.

The technic just described was at first employed only in favorable cases, but gradually I have come to use it with satisfaction as a routine, except in the presence of large, tightly impacted stones. Those stones present special problems. Before operation it may be impossible to gain a clear idea of the condition of the bladder, kidneys, and treatment is hampered by inability to drain the bladder by a urethral catheter. At operation, traction of the stone is sometimes extraordinarily difficult, especially if it is hourglass in shape with a constriction tightly grasped by the neck of the bladder. In such instances it has been found helpful to use the hands bimanually, with one finger in the bladder and a finger of the other hand under the sheets in the rectum. Since these bladders and stones are usually heavily infected, contamination of the incision can scarcely be avoided; consequently, it is best to drain the bladder surgically. I have never encountered a stone that could not be removed suprapubically, but there were several stones in the present series which probably could not have been removed successfully by any other route.

Postoperative Care.—The urethral catheter is connected to a rubber tube, which drains into a bottle beside the bed. Special care is taken to keep this drainage system working continuously and efficiently, otherwise the bladder may become distended and leak into the prevesical space. The bladder is not usually irrigated after operation, but abundant fluids are given to keep it flushed out. If all goes well, the suprapubic drain is removed on the third or fourth day after operation and the catheter on the fourth to the sixth day. Children whose incisions have healed by first intention may safely be let out of bed after a week. The urine

alkaline, should be rendered acid. Dietary and general hygienic measures are continued, and before discharge in the hospital the patient or his parents are given advice regarding the future diet and the intake of fluids.

RESULTS

Since the treatment just described was developed during a period of years, it was applied its entirety only to the more recent patients the present series. It is thus possible to compare the results of different operative techniques the same clinic.

In 12 patients the bladder was drained suprapubically after removal of the stones. Perhaps the condition of these patients was the most serious; at any rate, the results were comparatively poor. Hospitalization averaged sixty days, and an average of forty days was required before leakage of urine from the incision ceased entirely. All the patients had an uncomfortable, and some of them a stormy, convalescence. Two died.

In 36 patients the bladder was closed without drainage, although no particular care had been taken to avoid contamination of the wound with contents of the bladder. In some instances the bladder had been distended with fluid, which escaped when the viscus was opened; in others retained urine had been the source of infection, and in still others the infected bladder had been irrigated during operation. These patients were in the hospital an average of thirty-one days. In 70 per cent the wounds became infected to a greater or less extent, and 66 per cent had postoperative leakage of urine from the incision. Only 22 per cent had healing without leakage or infection. There were no deaths.

In 35 patients all the essential features of the treatment which I have described were successfully carried out. The average stay of these patients in the hospital was eighteen days; in 16 per cent the wounds showed some infection. 3 per cent leaked and 84 per cent healed with neither leakage nor infection. There were no deaths. My personal series included 18 of these patients, for whom the average time from operation to discharge from the hospital was eleven days; 1 of the wounds showed slight infection.

A fourth, miscellaneous, group included 2 patients who refused operation, 2 who were moribund on admission to the hospital and died without operation and about 40 seen early in the series for whom various methods, later abandoned, were tried.

Urinary incontinence did not occur postoperatively in any case.

The operative mortality for the entire series, which represents the work of nine general sur-

geons, including junior men of the resident staff, was 1.6 per cent.

Fortunately, autopsies were made on the 4 patients who died. One patient had bilateral hydro-ureter and hydronephrosis; 2 had bilateral pyelonephrosis, and the fourth had hydronephrosis on the right side and pyelonephrosis with multiple abscesses in the cortex, extensive perinephritic infection and beginning empyema on the left side. Lithotomy was attempted with 2 of these patients; the other 2 died without operation shortly after admission to the hospital, despite drainage of the bladder with a catheter. All 4 patients had tenderness in the lumbar region; 3 had fever, and none excreted more than a trace of phenolsulfonphthalein in two hours.

A number of adult convalescents were examined cystoscopically one to two weeks after operation. The bladders which had been closed as described showed smooth healing, with little or no reaction, whereas those closed in the conventional manner usually showed invagination of uncovered vesical muscle with some surrounding inflammatory reaction.

It was not possible to follow most of these patients after their discharge from the hospital. Since they left pleased and grateful and none returned with vesical symptoms, it may be assumed that few, if any, had recurrence of stone during the period covered by this study. There were 2 patients with recurrent stone in the present series, however, both patients having been operated on previously elsewhere. In 1 the stone obviously had formed around a silk suture, which was still attached to the bladder wall.

COMMENT

Neither perineal lithotomy nor the crushing operation was employed in the present series of patients. The former is a destructive procedure, which probably should be reserved for stones associated with prostatic disease (Young⁵). Litholapaxy was contraindicated in virtually every case because of stricture, small urethra, impaction, large stone, severe cystitis, spastic or contracted bladder or other conditions.

The method of treatment described in this paper does not contain many new features; its value lies rather in the application of well recognized surgical principles and the sequence of certain essential steps. Briefly these are: (a) accurate diagnosis, which includes not only the demonstration of stones but an appraisal of the

5. Young, H. H.: *Practice of Urology*, Philadelphia, W. B. Saunders Company, 1926, vol. 1, p. 368; vol. 2, pp. 335 and 405.

condition of the entire urinary tract and of the body as a whole; (b) unhurried preoperative treatment which aims toward lessening intravesical infection, improving renal function and bettering the general condition of the patient; (c) suprapubic lithotomy without contamination of the wound; (d) anatomic closure of the bladder without suprapubic drainage; (e) continuous drainage of the bladder for four or five days by means of a urethral catheter, and (f) attempts during the postoperative period to bring the patient and his urinary tract back as nearly as possible to normal.

The results of lithotomy have been reported for the most part in the older literature. Watson and Cunningham,⁶ in a study of nearly 34,000 collected cases, found for children a mortality of 7.4 per cent for suprapubic lithotomy, of 3.3 per cent for perineal lithotomy and of 1.7 per cent for litholapaxy; for adults there was a somewhat higher mortality with all three types of operation. These authors pointed out that as a rule in the more difficult cases the patients come to suprapubic operation, a fact that should be kept in mind when mortality rates are compared. In the series at the Canton Hospital⁷ the mortality rate was 7.8 per cent for the suprapubic operation, 7.9 per cent for the perineal operation and 9 per cent for the crushing operation. Cabot⁷ reported a mortality of 10 per cent for suprapubic lithotomy for children under 14 years and an even higher per cent for adults. Olpp and Kuhne⁸ reported a total mortality of 7.2 per cent; Roys,⁸ 18.7 per cent, and Cochran⁹ 3.9 per cent. Joly⁹ had a mortality of 2.2 per cent from litholapaxy. Walker's large

personal series¹⁰ from India and England showed an over-all mortality of 3.87 per cent for three types of operation. Much of this was done in China or India on advanced conditions under unfavorable circumstances, before the introduction of modern physiological concepts of preoperative and postoperative care. Obviously it would be unfair to compare results in my small series with those just on the other hand, my results should be compared indiscriminately with those of litholapaxy in selected, early, uncomplicated cases of vesical stone.

A favorable showing is made, however, by the method here recommended from the point of view of length of hospitalization, healing of wounds without infection or leakage and absence of other postoperative complications. This procedure is applicable in all cases of vesical calculus and in more than 80 per cent of cases of the advanced condition, such as described in this report.

SUMMARY

Calculus of the bladder is endemic in Shantung Province, in northern China. This report is based on a study of 126 patients admitted to a small general hospital during a five year period.

The peculiar characteristics of incidence of vesical stone in that locality suggest a dietary factor in the pathogenesis.

Most of the patients had a far advanced condition; many were recognized as poor surgical risks.

The results of the treatment employed, as described in detail, on the whole were satisfactory. Many patients had an uncomplicated convalescence, with primary healing of the suprapubic incision. The operative mortality for the entire series was 1.6 per cent. Recurrences were observed.

Salt Lake General Hospital.

6. Watson, F. S., and Cunningham, J. H.: *Diseases and Surgery of the Genito-Urinary System*, Philadelphia, Lea & Febiger, 1908, vol. 1.

7. Cabot, A. C.: *Stone in the Bladder*, in Keen, W. W.: *Surgery*, Philadelphia, W. B. Saunders Company, 1916, vol. 4, p. 347.

8. Roys, C. K.: *The Choice of Operation for Vesical Calculus*, *China M. J.* 24:259, 1910.

9. Joly, cited by Herman, L.: *The Practice of Urology*, Philadelphia, W. B. Saunders Company, 1938, p. 841.

10. Walker, J. W. T.: *Operations for Vesical Calculus*, in Burghard, F. F., and Kanavel, A. B.: *On Loose-Leaf Surgery*, New York, Oxford University Press, 1920, vol. 3, pt. 2, p. 714.

MASKED TRAUMATIC RUPTURE OF THE SPLEEN

JOSEPH K. NARAT, M.D., AND ANGELO L. VINCENTI, M.D.

CHICAGO

AND

ARTHUR F. CIPOLLA, M.D.

CICERO, ILL.

Rupture of the spleen occurs, according to ¹, with 30¹ to 47.6² per cent of contusions of the abdominal viscera. In view of this relatively high frequency of the condition it is essential for every surgeon to be familiar with signs and symptoms. Inasmuch as the mortality for ruptured spleen, ranging from 93³ to 100 per cent,⁴ can be reduced by an operation to 1 per cent,^{4d} it is self evident that early recognition of the injury is imperative, so that surgical intervention can be instituted without delay.

For practical purposes, two clinical pictures of traumatic rupture of the spleen may be distinguished:

1. The initial injury produces a rapidly progressive hemorrhage, with the following symptoms and signs, in descending order of frequency⁵: generalized abdominal pain, 100 per cent; tenderness, 95 per cent; rigidity, 85 per cent; shock, 65 per cent; dullness on percussion, 60 per cent; vomiting, 35 per cent; localized tenderness, 30 per cent, and abdominal distention, 15 per cent. A history of trauma to the left upper quadrant of the abdomen combined with the aforementioned signs is strongly suggestive of rupture of the spleen.

Few signs are pathognomonic of rupture of the spleen. Irritation of the left side of the

diaphragm by accumulation of blood may cause abdominal pain with radiation to the left scapula (Kehr's sign). Roentgenograms may reveal increased density in the affected region and abnormal elevation of the left side of the diaphragm, in addition to displacement of the stomach to the right or compression of the fundus. Palpation discloses a tender, indefinite mass in the left upper quadrant of the abdomen. Dullness on percussion may be present not only in the left upper quadrant and the left flank but in the right flank; on the shifting of position the dullness in the right flank disappears (Ballance's sign).

The differential diagnosis should consider fracture of the lower ribs on the left side, traumatic pleurisy, laceration of the liver or the left kidney, rupture of a hollow viscus and ectopic pregnancy. Simple contusion of the abdominal wall without injury of the internal organs does not affect the pulse rate, the blood pressure or the blood cell count. In doubtful cases Wright and Prigot² advocated diagnostic tapping of the abdomen.

2. After recovery from the initial injury, which may be trifling, an asymptomatic or latent period is followed by a delayed, recurrent hemorrhage (*hémorragie en deux temps*). The usually abrupt onset of the secondary hemorrhage initiates a clinical syndrome consisting of abdominal pain, rigidity and tenderness, soon followed by shock or collapse. However, the secondary hemorrhage may not start dramatically with acute symptoms of loss of blood but may have an insidious onset.

Zabinski and Harkins^{4d} stated that the ratio of incidence of delayed to immediate grave hemorrhage is 1 to 6. Great diagnostic difficulties are encountered in cases of delayed splenic hemorrhage. The apparent well-being of the patient during the latent period may create a false sense of security and may cause the attending physician to minimize the gravity of the situation.

The case to be reported is an instance of delayed splenic hemorrhage. For the sake of brevity only the most pertinent facts are mentioned.

From the St. Elizabeth Hospital.

1. Mazel, M. S.: Illinois M. J. 62:170, 1932.
2. Wright, L. T., and Prigot, A.: Traumatic Subcapsular Rupture of Normal Spleen, Arch. Surg. 39: 551 (Oct.) 1939.
3. Berger, E.: Arch. f. klin. Chir. 68:768, 1902.
4. (a) McIndoe, A. H.: Brit. J. Surg. 20:249, 1932. (b) Puestow, C. B.: S. Clin. North America 20:195, 1940. (c) Roettig, L. C.; Nusbaum, W. D., and Curtis, G. M.: Am. J. Surg. 59:292, 1943. (d) Zabinski, E. J., and Harkins, H. N.: Delayed Splenic Rupture: Clinical Syndrome Following Trauma; Report of Four Cases with Analysis of One Hundred and Seventy-Seven Cases Collected from Literature, Arch. Surg. 46:186 (Feb.) 1943. (e) Webb, R. C.: Journal-Lancet 59:545, 1939. (f) Bailey, H. A., and Schreiber, S. L.: Am. J. Surg. 66:4, 1944. (g) Wright and Prigot.²
5. Foster, J. M., and Prey, D.: Am. J. Surg. 47: 487, 1940.

REPORT OF A CASE

Mrs. S. F., aged 24, fell on an icy sidewalk on Dec. 24, 1944 and struck her left flank against the curb. The pain experienced in the abdomen ceased after a few minutes, and only a slight ache remained. On the following two days the patient went about her work and forgot the initial injury; on the evening of December 26 she ran against a doorknob, which struck the left side of her abdomen. After this accident the pain became more accentuated; one hour later the patient fainted but regained consciousness within a short time. She had a moderate amount of pain during the following night and entered the St. Elizabeth Hospital on the morning of December 27. Soon after admission she vomited and had diarrhea.

Her past history was irrelevant. At the time of the first examination she did not appear acutely ill and did not offer any complaints of pain. The routine physical examination revealed essentially no abnormality. The temperature was 98.6 F.; the pulse was of good quality, with a rate of 96; the respiratory rate was 24, and the blood pressure was 98 systolic and 64 diastolic. The abdomen was neither rigid nor distended, and only a slight tenderness was present on pressure on its upper portion. The blood count showed 2,860,000 red cells, 13,000 white cells, 83 per cent neutrophils and 17 per cent lymphocytes. The hemoglobin content was 9.8 Gm. (Hayden-Hauser).

The roentgenogram revealed no air under the diaphragm.

In spite of the fact that there was no rigidity or marked tenderness of the abdominal wall and none of the common signs of acute hemorrhage, such as pallor, air hunger, cold and clammy skin, progressive increase in the pulse rate or decline of the systolic blood pressure, the low red cell count, together with a history of two traumas of the left upper quadrant of the abdomen, a fainting spell and vomiting, suggested rupture of the spleen.

With the patient under pentothal sodium anesthesia administered intravenously, the abdomen was opened through an upper midline incision. Liquid blood and several large clots were distributed throughout the peritoneal cavity. Approximately 250 cc. of blood was aspirated during the operation, and a considerable amount was removed with sponges. Inspection of the spleen disclosed a tear through the hilus, splitting the entire organ in two. The bridge connecting the two parts was approximately one-half the thickness of the organ. Blood was seen spurting from the splenic artery. Splenectomy was performed in the usual manner, and the abdomen was closed without drainage. Blood was obtained from a donor, and therefore the blood aspirated from the abdomen was not used for an auto-transfusion. One hundred thousand units of penicillin was administered in five doses, the first before and the remaining four after the operation. The patient made an uneventful recovery.

The pathologic report was as follows: The specimen consisted of a spleen which weighed about 150 Gm. and measured 10 by 7 by 4 cm. Through the middle there was an irregular transverse tear, 5 cm. long, which almost cut the spleen in half and went through the attachment of the vessels.

On the third postoperative day the blood count showed 4,050,000 red corpuscles and 13,000 leukocytes, of which 86 per cent were neutrophils, 10 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils.

COMMENT

The interesting point in this case is that the patient sustained two traumas eight hours apart. It is a matter of conjecture which accident caused the rupture of the spleen. Probably the first accident was responsible for the laceration, while the second dislodged the hematoma, creating a secondary hemorrhage. The main reason for reporting this case is the low erythrocyte count, which increased the suspicion of internal hemorrhage, in spite of the fact that the customary clinical signs of rupture of the spleen were nearly completely missing. This observation is at variance with Babcock's statement that with rupture of the spleen there is an early and rapid increase in leukocytes with a relative fall in hemoglobin and the red cell count.

The lesson to be drawn from this observation is the advisability of repeated blood cell counts in cases of contusion of the upper portion of the abdomen. Even if no clinical manifestation of a ruptured spleen are present, a falling erythrocyte count should be considered a warning signal, and an exploratory laparotomy should be performed without delay.

The diarrhea which occurred in our patient may possibly be explained by Bailey and Selber's hypothesis that the blood escaping from the lacerated spleen irritates the splenic flexure and the descending colon with production of contraction, thus causing loose bowel movements.

SUMMARY AND CONCLUSIONS

In the case reported, the patient sustained two successive insignificant traumas; the only sign observed during the latent period was a low erythrocyte count, which led to the diagnosis of a ruptured spleen. The diagnosis was confirmed by operation.

In a case in which there is a history of contusion of the left upper quadrant of the abdomen, the possible presence of a ruptured spleen should be borne in mind. It must be stressed that the clinical picture of an intraperitoneal hemorrhage may be deceiving and that a low erythrocyte count in such a case is a valuable diagnostic aid. Failure to recognize the condition may be responsible for a fatal outcome; therefore an exploratory operation should be performed without delay, even if no sign other than a low red cell count is present.

1200 North Ashland Avenue, Chicago

718 South Kedzie Avenue, Chicago.

1234 South Fifty-First Avenue, Cicero, Ill.

6. Babcock, W. W.: *Principles and Practice of Surgery*, Philadelphia, Lea & Febiger, 1944, p. 172.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1943

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN ACADEMY
OF ORTHOPAEDIC SURGEONS

XVIII. AMPUTATIONS, APPARATUS AND TECHNIC

PREPARED BY J. WARREN WHITE, M.D., GREENVILLE, S. C.

Amputations.—As would be expected during wartime, many articles on amputations have appeared. Nothing particularly new has been published, but ten or a dozen papers discuss the value of refrigeration as an appropriate anesthetic, particularly for extremely ill patients and for those in whom serious vascular disease exists, with or without gangrene.⁶⁰⁶ Kennedy⁶⁰⁷ emphasizes its importance in military service and in civilian practice, where it is so valuable in diabetic gangrene and vascular disease. Allen and Crossman⁶⁰⁸ state the belief that thrombotic and embolic accidents are reduced by the use of refrigeration. The death rate in their cases has fallen from 60 to 15 per cent as the result of using refrigeration. The general consensus is that healing is to some degree retarded when refrigeration is employed, but to no serious extent, notwithstanding popular lay articles to the contrary, such as the brief paper by Doane,⁶⁰⁹ which otherwise is a well worth while exposition of the subject in nontechnical language for hospital administrators. A successful amputation is reported by Dziob and Brown,⁶¹⁰ with complications of sepsis and a temperature of 108.4 F., for which refrigeration seemed particularly appropriate. The high temperature was attributed to a reaction to sulfathiazole, however, rather than to the sepsis. Johnson⁶¹¹ also reports a reduced mortality rate for amputations as

a result of refrigeration anesthesia as compared with other anesthesia.

One author⁶¹² erroneously refers to refrigeration when he discusses anesthesia by freezing. Of course if actual freezing takes place real damage to the tissue ensues. This cannot occur if plain chipped ice is employed. One of the dangers, however, of using a positive refrigeration machine is that actual freezing might accidentally occur. No article in 1943 discusses the use of a mechanical refrigerator.

All articles except one recommend the use of refrigeration before the application of a tourniquet and are in agreement about the time necessary to allow the application of a painless tourniquet and the production of complete anesthesia in an extremity. Most articles recommend continuing the refrigeration of the stump from a few hours to a few days. Two articles⁶¹³ recommend that the icing be discontinued after the operation, and one of them^{613a} does not even advocate refrigeration before application of a tourniquet. This seems reasonable, as the application of a broad tourniquet is not particularly painful. [ED. NOTE.—I suggest that those who are interested try it on themselves to note how relatively painless it is.] Use of a properly arranged rubber sheet on a bed which is slightly raised at one end is recommended instead of the cumbersome ice box in an article by Glasser and Mersheimer,^{613a} who make some other practical suggestions. They see no advantage in using iced instruments. [ED. NOTE.—I feel that this is the best article on a practical technic that has appeared, and I urge the surgeon who is considering the use of refrigeration to read it.]

For patients who are debilitated by a gangrenous extremity, Haley⁶¹⁴ recommends elimination of the circulation in the involved extremity by

606. Pouliot, A.: Anaesthesia by Local Refrigeration in Case of Amputation for Gangrene of Lower Extremity, *Union méd. du Canada* 72:408-410 (April) 1943.

607. Kennedy, J. A.: Technic and Device for Application of Ice Anesthesia for Amputation of Extremities, *U. S. Nav. M. Bull.* 41:226-230 (Jan.) 1943.

608. Allen, F. M., and Crossman, L. W.: Refrigeration in Amputations for Gangrene, *Tr. A. Am. Physicians* 57:320-325, 1942.

609. Doane, J. C.: Proof of Practicability of Refrigeration Anaesthesia, *Mod. Hosp.* 60:64-65 (May) 1943.

610. Dziob, J. M., and Brown, R. K.: Reduced Temperature Anaesthesia for Surgery of Trauma, *Indust. Med.* 12:79-80 (Feb.) 1943.

611. Johnson, M. D.: Experience in St. Louis with Refrigeration Anaesthesia, *Mod. Hosp.* 60:65 (May) 1943.

612. Nixon, E. A.: Amputation Anaesthesia by Freezing, *Northwest Med.* 42:131-133 (May) 1943.

613. (a) Glasser, S. T., and Mersheimer, W. L.: Refrigeration Anaesthesia of Extremities, *Am. J. Surg.* 62:231-234 (Nov.) 1943. (b) Stevenson, J. A. F.: Reduced Temperature in Surgery, *McGill M. J.* 12:36-39 (Feb.) 1943.

614. Haley, E. R.: Arteriosclerotic Gangrene, *Arch. Surg.* 46:518-524 (April) 1943.

application of a tourniquet just below the knee after a half-hour's chilling. The leg distal to this point is then refrigerated for the three or even four days necessary to bring the patient to an optimum condition for amputation. Eight hours before amputation the leg is chilled with chipped ice to the upper third of the thigh, and a half-hour later a second tourniquet is applied 1 inch (2.5 cm.) or so distal to the top of the chilled area. A drawing of the simple but apparently efficient ice box accompanies the article. The management of 4 typical cases is presented in detail.

Evidently stimulated by the success of the use of cold in amputations, two authors discuss the value of cold as a therapeutic agent to relieve pain. Rupp⁶¹⁵ recommends its use for compound fractures, gunshot wounds, crushing injuries and severe infections such as those due to the gas bacillus and suggests its use in military surgical procedures, even in the field, in view of the development of an efficient 200 pound (90.7 Kg.) refrigeration unit. Krieg⁶¹⁶ calls attention to the use of cold as heat is ordinarily used to relieve pain, particularly in combating postoperative pain. He states that in addition to relief from pain there seems to be diminution in the development of complications.

Muirhead, Kregel and Hill⁶¹⁷ report an interesting series of experiments on dogs in which the value of plasma in addition to the amputation of frozen extremities is demonstrated. In a group of 10 dogs from which the limb was removed three and a half hours after freezing, 8 died of shock. In another group, in which replacement of plasma was the only treatment used, all 10 lived, while in a third group, in which replacement of plasma was used with amputation, all 10 lived. This article demonstrates the need of adequate surgical operation in addition to replacement of plasma.

The danger of using a tourniquet on an injured extremity is noted by Blalock⁶¹⁸ in experiments on dogs. He found that refrigeration of ischemic extremities during the time the tourniquet is applied definitely minimizes the damage. [ED. NOTE.—Here is another proof of the value of cold in saving tissue by reducing its metabolic requirements.]

615. Rupp, N. H.: Modern Concepts of Refrigeration Anesthesia, *Anesth. & Analg.* 22:46-51 (Jan.-Feb.) 1943.

616. Krieg, E. G.: Control of Postoperative Pain, *Am. J. Surg.* 62:114-116 (Oct.) 1943.

617. Muirhead, E. E.; Kregel, L. A., and Hill, J. M.: Therapy of Shock in Experimental Animals, *Arch. Surg.* 47:258-282 (Sept.) 1943.

618. Blalock, A.: Effects of Lowering Temperature of Injured Extremity to Which a Tourniquet Has Been Applied, *Arch. Surg.* 46:167-170 (Feb.) 1943.

The value of pressure dressings, such as are applied to burns, to severely frozen limbs of dogs is shown by a series of experiments performed by Fell and Hanselman.⁶¹⁹ They give further evidence of the value of immobilization in addition to the value of circulatory support together with protection of superficial structures.

The Callander amputation with the Pearl modification is discussed by Grodinsky,⁶²⁰ who feels that the flaps of skin are too long and the bed of the patella can be too easily misplaced. He advises against the use of a drain and against the dressing of the wound before seventy-two hours.

The old argument for and against end-bearing stumps is discussed again by Harris,⁶²¹ who, with much evidence to substantiate his contentions, upholds the Canadian opinion relative to the value of end-bearing stumps. He compares the favorable results of 130 Stokes-Gritti amputations with the results of 233 amputations through the thigh and the satisfactory outcome of 60 Syme amputations with the outcome of twice as many amputations below the knee. [ED. NOTE.—In spite of these results, one of us feels that for the occasional amputator non-weight-bearing stumps are to be recommended, as the patients and the manufacturers of limbs have least trouble with these. The added skill required to produce a satisfactory end-bearing stump is too great for the procedure to be popular with the average surgeon. The makers of limbs also are able to make better fitting limbs for the non-weight-bearing stumps, at least in the United States. However, my choice would be, if necessary, an end-bearing stump, but it is certain that I should go to a surgeon like Harris, who is enthusiastic about them. It is an excellent article, which should be read by even the occasional amputator.]

Another experienced Canadian amputator, LeMesurier,⁶²² reviews once more, in an excellent article, most of the important points on amputations needing emphasis, including controversial subjects such as the treatment of nerve endings, the value of end-bearing stumps and the use of temporary limbs.

Pearl and Misrack⁶²³ discuss anew the value

619. Fell, E. H., and Hanselman, R.: Prevention of Shock and Death by Immediate Application of a Pressure Dressing, *Ann. Surg.* 117:686-691 (May) 1943.

620. Grodinsky, M.: Modification of Callander Amputation, *Surg., Gynec. & Obst.* 76:337-340 (March) 1943.

621. Harris, R. J.: Amputation-Stumps, *Whelan M. J.* 41:1086-1090 (Dec.) 1942.

622. LeMesurier, A. B.: Amputation Stumps, *J. Bone & Joint Surg.* 25:566-575 (July) 1943.

623. Pearl, F., and Misrack, M.: Atraumatic Amputation Through Lower Thigh, *Surg., Gynec. & Obst.* 77:354-359 (Oct.) 1943.

of the Pearl modification of the Callander operation, particularly as regards its use in peripheral vascular disease, but no new points are brought out. They simply emphasize the so-called atraumatic technic, which avoids cutting through muscle tissue.

Bickel and Ghormley⁶²⁴ emphasize the value of amputations below the knee in occlusive arterial disease and do not feel that they are as hazardous as commonly believed. They admit that good surgical judgment, which really means experience, is necessary, and here again it is brought out for the occasional amputator who has to make up his own mind that an amputation below the knee is a much more radical procedure than a classic amputation through the thigh. In other words, this is a paper for a surgeon well experienced in occlusive vascular disease and amputations. Of 110 cases in which amputation below the knee was done at the Mayo Clinic in the last eleven and one-half years for this condition, in only 20 was reamputation above the knee found necessary.

Breed and Mulholland⁶²⁵ have written a comprehensive paper on amputations, which includes some controversial points but which brings out nothing particularly new. Refrigeration anesthesia, prevention of thrombosis and local instillation of sulfonamide drugs are discussed.

An excellent paper which urges delay in amputation for extensive organic arterial occlusion, pending improvement of the patient's condition, has been written by Theis.⁶²⁶ He also calls attention to the futility of minor amputations.

Amputations for gas gangrene are discussed in an article in the *Bulletin of War Medicine*,⁶²⁷ and the following important points are stressed: 1. The spread of infection in muscle is longitudinal and not from group to group, so that a longer stump is made possible by the removal of individual infected muscle tissue above the point of section of the bone. 2. Flaps of skin may be fashioned with actual crepitus present but should not be sutured. 3. Changes in the color of the skin do not indicate the extent of the subjacent infection. 4. Guillotine operations are satisfactory only if immediate traction of the skin is possible.

624. Bickel, W. H., and Ghormley, R. K.: Amputations Below the Knee in Occlusive Arterial Disease, *S. Clin. North America* **23**:982-994 (Aug.) 1943.

625. Breed, E. S., and Mulholland, J. H.: Amputation in Relation to Extremity Injuries, *S. Clin. North America* **23**:534-555 (April) 1943.

626. Theis, F. V.: Amputation for Advanced Arterial Disease, *Surg., Gynec. & Obst.* **76**:35-40 (Jan.) 1943.

627. Amputations for Gas Gangrene, abstracted, *Bull. War Med.* **3**:492 (May) 1943.

Two articles on transiliac amputation have been abstracted but do not have enough new material in them to warrant separate comment, and the reader particularly interested is referred to the original articles.⁶²⁸

Shimberg,⁶²⁹ writing from the headquarters of the Veterans' Administration, discusses in a rather extensive article a program for the amputee from the time of his amputation to his complete rehabilitation, showing how the Veterans' Bureau is planning to take care of the handicapped military personnel. It has evidently been written as a guide or blue print, particularly for centers where amputations are performed.

Two articles,⁶³⁰ one of them by Kessler, have appeared during 1943 on kineplastic amputation of the forearm, showing that some surgeons are still doing this highly technical procedure, which should be reserved for those who do this operation routinely.

Maynard⁶³¹ describes disarticulation of a hip joint in which instead of the conventional ligation of the femoral artery in the groin at the start a double subcutaneous tourniquet is pulled through a stab wound on the inner aspect of the thigh from a trochanteric wound an inch (2.5 cm.) below the groin. One part of the rubber tubing is brought around in front to include the femoral vessels, and the other half is passed around the back to surround the gluteal vessels. After the ends of the tube are fastened together tight enough with clamps, the amputation is done in the usual manner, the large vessels being picked up and ligated as they are encountered. [Ed. NOTE.—I, after having done several disarticulations of the hip joint in the conventional manner, i. e. by ligating the femoral artery at the start, see no particular advantage in Maynard's method, but it is mentioned here as it was thought that its novelty might appeal to others.]

An important discussion on amputations in children has been written by vom Saal,⁶³² who recommends epiphysial fusion to avoid the protrusion of bone from the end of the stump.

628. King, D., and Steelquist, J.: Hip, Tumors, Transiliac Amputation, *J. Bone & Joint Surg.* **25**:351-367 (April) 1943. Fernández Fierro, D.: Interilio-sacro-pubic Disarticulation, *J. Internat. Coll. Surgeons* **6**:368-374 (July-Aug.) 1943.

629. Shimberg, M.: What Shall Be Done for the Amputé? *M. Bull. Vet. Admin.* **19**:428-432 (April) 1943.

630. Adams, J. D.: Kineplastic Amputation of Forearm, *New England J. Med.* **229**:466-468 (Sept. 16) 1943. Kessler, H. H.: Cineplastic Operation in Rehabilitation of Amputation Cases, *Mil. Surgeon* **93**:281-285 (Sept.) 1943.

631. Maynard, R. L.: Hip-Joint Disarticulations, *Tr. New England S. Soc.* **24**:248-256, 1941.

632. vom Saal, F.: Amputations in Children, *Surg., Gynec. & Obst.* **76**:709-710 (June) 1943.

[Ed. NOTE.—I have not had much experience along this line, but in the few cases that have come under my observation I have not had this complication and wonder if the ends of the bone were properly covered at the start. I recently saw two stumps, two and four years after amputation, that were giving no trouble.]

Apparatus.—The description of a new portable, dismountable pelvic support was published in Brazil⁶³³ in 1942. The device has, as far as can be noted, no particular advantage over those of a similar nature which have already been devised to hold a pelvis with ease while plaster bandages are applied.

The use of wood instead of metal in the making of a Bohler-Braun frame, designed with certain modifications, is recommended by Nickerson.⁶³⁴ One wonders during these days of metal shortage why more apparatus, even Thomas splints, have not been made of wood, in spite of its lack of strength and durability.

Hauser and Martin⁶³⁵ have devised a simplified fracture table of wood, which apparently has served well. Detailed drawings are shown. A few bolts and a shelf bracket are the only metal fittings used. The table can be easily assembled at any station hospital with scrap lumber.

Also in view of the scarcity of metals Dudgeon and Rike⁶³⁶ have devised an inexpensive portable wood fracture table. Any one who is contemplating making one should certainly peruse these two articles, as they are both well illustrated, and in Dudgeon and Rike's article even the size and the quantity of lumber are given.

Appreciating the drawbacks of the permanently applied Bohler "walking iron" cast, Lawson⁶³⁷ recommends a detachable wooden sole, or sabot, as he calls it, which can be removed at night and which has many other advantages. It is attached like a roller skate except that straps are used both in front and in back.

[Ed. NOTE.—I recall seeing just such an arrangement in Putte's clinic in 1935, which I

adopted and have been using ever since, especially as a lift to discourage weight bearing on a extremity that needs protection (coxa plana). An improvement even on this sabot has been suggested by Stamm,⁶³⁸ who attaches a runner to the bottom of the wooden shoe order that some of the thrust in walking may be taken up. This would be particularly suitable for building up a short leg. [Ed. NOTE.—I distinctly recall such an apparatus put out commercially.]

Still another "walking iron," almost identical to Putte's, has been constructed entirely of wood by Clark,⁶³⁹ a Britisher, and it strap on. He calls it rather appropriately a "rocker."

With the discrediting of Sister Kenny's policy of discouraging accurate evaluation of muscle strength, a simple muscle-testing board devised by Brown and Thompson⁶⁴⁰ is worth noting and looking into by those who are interested in portable and can be used both in bed by the short legs or in the usual way, as designed.

A skeletal support applied to the ilium behind the anterior superior spine on both to prevent decubitus in paraplegia, is described by Westhues⁶⁴¹ of Germany; it is well considering for some patients with tra lesions of the spinal cord, who are so difficult to handle. To simplify the method, the author suggests a special pelvic caliper. He states the apparatus has been left in place for as fifteen weeks without injury to the patient. This apparatus will be appreciated by those who have too often felt the need of such a device.

An improvement on the simple forearm stabilizer is a full radius half ring; it is on a swivel and encircles just below the elbow. The hand grips the palm a little better and simulates a pistol grip to give better control. Claims that falls from the loss of crutch are almost unknown. [Ed. NOTE.—I felt that this special attention to crutches is a dearth of artificial limb attachments as a Thomas ring splint

633. de Araujo, A.: Portable and Dismountable Pelvis Support, *Rev. brasil. de ortop. e traumatol.* 3: 271-274 (July-Aug.) 1942.

634. Nickerson, S. H.: Wooden Splint to Be Used in Skeletal Traction, *Bull. U. S. Army M. Dept.*, July 1943, no. 68, pp. 203-211.

635. Hauser, C. U., and Martin, W. F.: Simplified Fracture Table of All Wood Construction, *Mil. Surgeon* 93:313-317 (Sept.) 1943.

636. Dudgeon, H., Jr., and Rike, B. J.: An Inexpensive Portable Fracture Table, *J. Bone & Joint Surg.* 25:469-472 (April) 1943.

637. Lawson, J.: Device to Replace Walking Iron in Plaster Cases, *J. Roy. Army M. Corps* 81:39-49 (July) 1943.

638. Stamm, T. T.: New Walk-Leg Plasters, *Brit. M. J.* 2:13 (June) 1942.

639. Clark, C. D.: Walking "Iron," *Brit. M. J.* 2:364 (Sept. 18) 1942.

640. Brown, M. E., and Thompson, J.: A Simple Muscle-Testing Board, *Physiotherapy R.* 4:143 (April) 1943.

641. Westhues, H.: Half-Sphere Splint, *Bull. War Med.* 3:447 (July) 1942.

642. Stockmeier, H.: Ring Splint, *Arch. Klin. Chir.* 194:337 (March) 1943.

en devised by Hook and Mazet⁶⁴³ for application to fractures of the cervical portion of the spine when Cruchfield tongs for skeletal traction are employed. There are various obvious advantages, the particular one being that the vertical position of the body can be maintained at least part of the time and the patient therefore is more mobile; mobility is especially desirable in military combat areas.

Bisnoff⁶⁴⁴ has devised an apparatus which facilitates the care of extensive injuries to the jaw. The equipment is too complicated for description here, and the interested reader is referred to the original article. The outstanding advantage of the appliance is that it eliminates the need for specially constructed plaster head casts as supports for traction wires.

The useful anvil retractor of Blount⁶⁴⁵ for trochanteric osteotomy, which was shown in his excellent exhibit at the meeting of the American Academy of Orthopaedic Surgeons in 1943 in Chicago, has been recorded in orthopedic literature and is worthy of mention. [Ed. NOTE.—I have found after repeated use that the apparent excessive pressure on the tissues on the dorsum of the thigh does no harm, and it certainly does receive a great deal of the pounding during an osteotomy, which otherwise would be transmitted completely to the joint.]

Written for nurses but meriting the attention of surgeons, Calderwood's⁶⁴⁶ article on Russell traction can be better understood than the original article, which appeared over twenty years ago.

An ingenious and inexpensive apparatus, all in one piece, used as a combined adhesive tape "spreader" and preventer of foot drop has been devised by Baker and Reed.⁶⁴⁷ This device, while it allows active motion of the ankle and prevents foot drop, is an efficient "spreader" when traction with adhesive tape is employed.

The principle of the so-called well leg traction for trochanteric fractures, which was originally devised by Dr. Hoke, has been incorporated in

an apparatus for above the knee by Stein and Lewis,⁶⁴⁸ in order that motion in the knee can remain unrestricted. Single cross traction pins are drilled through both femurs an inch (2.5 cm.) above the condyles, which are immobilized in plaster casts, with a turnbuckle placed diagonally between the casts as a control. For those who do not wish to immobilize the knees, this equipment should be considered.

A transparent splint made of a substance resembling lucite (a polymer of the acrylic ester group of artificial resins) is described by a Britisher.⁶⁴⁹ It is similar to the splint experimented with but without success by the I. E. du Pont de Nemours Company. Its drawback is that the material has to be heated so high that a mold of the extremity has to be made rather than the splints being shaped to the part directly. This detracts seriously from its usefulness.

For orthopedic nurses particularly interested in restraint equipment for frames, Warren⁶⁵⁰ has written a detailed, well illustrated paper giving patterns for various types of apparatus, such as Bradford frames and chairs. This article should be remembered when present restraint apparatus seems inadequate.

Another article by McGoeys⁶⁵¹ along the same line, for reference particularly, is a description of a "T" binder, called a pelvic binder, simply a draping equipment for clinical work, which interferes a minimum amount with motion and observation. For persons not satisfied with their present method of draping, this article is recommended.

For the surgeon wishing to bring his Zander apparatus up to date, an article by Lanckenau⁶⁵² is recommended. In it she describes a standard metal unit suspension frame, which in itself is a portable gymnasium. The advantages of modern suspension exercise as compared with the older Swedish remedial exercise are enumerated. Four figures are a help for understanding this rather complicated piece of equipment, which, however, takes up much less room than the old equipment, an important advantage when office floor space is at such a premium.

643. Hook, F. R., and Mazet, R., Jr.: Ambulatory Traction Device for the Treatment of Fractures of the Cervical Spine, U. S. Nav. M. Bull. 41:207-213 (Jan.) 1943.

644. Bisnoff, H. L.: Fractures of the Jaws: External Traction Appliance, Am. J. Orthodontics (Oral Surg. Sect.) 29:96-101 (Feb.) 1943.

645. Blount, W. P.: The Anvil-Retractor, J. Bone & Joint Surg. 25:208-210 (Jan.) 1943.

646. Calderwood, C.: Russell Traction, Am. J. Nursing 43:464-469 (May) 1943.

647. Baker, L. D., and Reed, F. J.: Self Adjusting Foot Piece for Preventing or Correcting Equinus Deformity When Traction Is Applied to a Lower Extremity, J. Bone & Joint Surg. 25:680-682 (July) 1943.

648. Stein, I., and Lewis, R. M.: Well Thigh Traction in the Treatment of Intertrochanteric Fractures, Am. J. Surg. 59:509-512 (March) 1943.

649. MacGowan, T. J. B. A.: Plastic Splints, Lancet 1:805-806 (June 26) 1943.

650. Warren, O. E.: Orthopedic Restraint, Am. J. Nursing 43:831-832 (Sept.) 1943.

651. McGoeys, P. F.: Pelvic Binder, Brit. M. J. 1:647 (May 29) 1943.

652. Lanckenau, N. I.: Rehabilitation by Modern Methods of Exercise, Brit. J. Phys. Med. 6:12-15 (Jan.-Feb.) 1943.

An instrument for opening the jaws has been devised by Hallam,⁶⁵³ which is obviously far superior to the usual racheted mouth gag; it exerts a force on many teeth rather than on one or two above and below. The only apparent difficulty is in getting it into mouths that are closed or almost closed, as it is evidently a more bulky apparatus than the usual screw or gag.

Brenner⁶⁵⁴ describes a traction apparatus similar to but possibly less cumbersome than the Soutter distraction equipment, which appeared many years ago. It is particularly applicable to the lower part of the leg rather than to the upper extremity, to which the Soutter equipment is more adaptable. It is, its originator states, particularly suitable for fluoroscopic work.

Barnard⁶⁵⁵ has devised a special surgical table top which is arranged to facilitate the taking of direct lateral roentgenograms of the hip. For the anteroposterior view the usual tunnel is employed, into which the cassette can be slid. An indentation in the side of the 2 inch (5 cm.) thick table top at the level of the trochanter permits the cassette, which is covered with a sterile drape, to be slipped in vertically, so that a lateral roentgenogram can be taken without moving the hip. The article is well illustrated.

Technic.—New Surgical Instruments: A foreign body finder, or "diviner," for locating metallic objects in wounds, which functions on an electrical principle, has been devised by Moorhead.⁶⁵⁶ Its specific advantages are (1) portability (about the size of a small radio) and adaptability to any electrical source; (2) ability to be used as an accessory to fluoroscopic and roentgenographic examination or without them; (3) ability to be used within a wound; (4) responsiveness to nonmagnetic as well as to iron or steel objects; (5) ease and certainty of application. It was first used in Honolulu after the attack on Pearl Harbor, when twenty-one fragments were removed on two successive days.

A self-locking retractor, or better a spreader, for arthrodesis is described by Castillo Odena,⁶⁵⁷ which is devised particularly for the subastragalar joint but is claimed to be useful in exposing cartilages of the knee, although the

translator does not mention cartilages of knee joint specifically. [Ed. NOTE.—It is gretted that further information about this strument is not available, as the report is written in Spanish and appeared in a jour which was not accessible to me.]

A specially designed bone punch for center plate screw holes through bone is reported Capener,⁶⁵⁸ which allows the proper center of all the drill holes beneath a plate evenly give it the greatest strength possible.

Adams,⁶⁵⁹ a London surgeon, has devised another instrument for determining the depth a screw hole in bone so that a screw of proper length can be selected. [Ed. NOTE.—Many these instruments have appeared, but one wonders why a simple crochet hook is not practical as good as a special instrument or even an intravenous needle of sufficient length and with the end turned enough to catch the edge of the bone at the distal end of the hole.]

Mitchell,⁶⁶⁰ another Britisher, describes a knife devised to facilitate the removal of cartilages in the knee; it is similar to Lowe and Breck's knife, which was described six years ago. [Ed. NOTE.—I have tried with little success to use this knife; it seems too large for most knees.]

Another expansion reamer for the acetabulum has been designed by Kleinberg,⁶⁶¹ who claims that (1) it is light in weight but strong; (2) it is easily adjustable, and (3) it has a large handle. For those who are dissatisfied with their present reamer, it is suggested that they examine this one.

Basom and Breck⁶⁶² have written a paper advocating the use of a commercial subcaliber electric drill geared down from the usual high speed. [Ed. NOTE.—It is felt that its only advantage is price, as it is feared that a cheap commercial drill could not stand up under constant use, particularly if it is geared down to the speed at which the bearings would be strained by the resultant increased power, for which housing, etc., are not designed. For occasional use, such as drilling in pins, it might be all right, but it would be more likely to fail at a crucial time and be more expensive in the long run. For an emergency it would be useful.]

653. Hallam, J. W.: A Gag for Dysfunction of Temporo-Mandibular Joint Following Mandibular Injury, *Brit. M. J.* 1:569 (May 8) 1943.

654. Brenner, F. T.: New Mechanical Fracture Spreader, *Am. J. Surg.* 59:141-142 (Jan.) 1943.

655. Barnard, V. L.: New Surgical Table Top and Cassette Holder for Surgical Roentgenographic Examination of the Hip, *Radiology* 40:599-602 (June) 1943.

656. Moorhead, J. J.: Foreign Body Finder: The Locator, *J. A. M. A.* 121:123-125 (Jan. 9) 1943.

657. Castillo Odena, I.: Self-Locking Retractor for Arthrodesis. *Bo. y trab., Soc. argent. de cirujanos* 4: 470-471, 1943.

658. Capener, N.: Punch for Use in Plating Fractures, *Lancet* 2:415 (Oct. 2) 1943.

659. Adams, J. C.: Screw Length in Bone Grafts, *Lancet* 2:415 (Oct. 2) 1943.

660. Mitchell, A.: Meniscotomy Knife, *Lancet* 1:157 (April 24) 1943.

661. Kleinberg, S.: Expansion Reamer, *Ann. Surg.* 116:957-959 (Dec.) 1942.

662. Basom, W. C., and Breck, L. W.: Improved Electric Drill, Saw and Kirschner Wire Drill, *Ann. J. Surg.* 60:151-153 (April) 1943.

routine use a light weight commercial motor, altered as suggested, would be far from satisfactory.]

One new advantage of vitallium is cited by an "ashman, Vere-Hodge,⁶⁶³ who states that its magnetic qualities make it particularly suitable for members of the British Royal Air Force, as compasses in the airplane would not be influenced if a pilot had a nonmagnetic plate in his arm.

Sutherland and Rowe⁶⁶⁴ are using metal plates for the repair of subluxated hips instead of bone, citing however only 3 operations. Two operations came out well, although the shelf was a little high in the roentgenograms. One plate was taken out because of sepsis. Walking was permitted four weeks after the operation, which seems to be far too early. Four more operations had been done since the original paper was written, but they had been done too recently to report the results. [ED. NOTE.—I feel that more experimental work should be done on this procedure before it is generally advocated.]

Another article describes a large vitallium cast of the upper quarter of the femur, approximating its normal shape, which was fitted over the shaft after the proximal end had been excised because of a neoplasm. In spite of various operative difficulties, it functioned well, and the patient died several years later of a heart attack. [ED. NOTE.—This report must describe the largest piece of vitallium ever used and serves as another demonstration of the tolerance of tissue for this inert material. Much credit must be given to the authors⁶⁶⁵ for this ingenious piece of work.]

The use of skeletal traction in correcting various severe deformities of the foot is discussed by Morris.⁶⁶⁶ While distraction might have been a better term, he has used a positive corrective device that is far superior to plaster casts, which are good for their success on tolerance of the skin pressure and which are more complicated. [ED. NOTE.—Some deformities need the tremendous force which is available with this method for correction, but one wonders if in most instances the actual sacrifice of bone to

obtain the desired correction of the foot might not be the better method.]

Another author⁶⁶⁷ cites the advantage of lucite caps in arthroplasty of the hip, because of their radiolucency and minimal irritability to the tissues. Their cheapness is also mentioned. Their use must still be considered in the experimental stage, and further reports will be looked forward to. One views with some concern, however, the long-lasting reaction to the constant chronic irritability of vitallium.

Thompson,⁶⁶⁸ in discussing osteotomy for the correction of angular disalignments, calls attention to the advantages of the telescoping V osteotomy in areas where the bone is conoid, such as the femoral trochanteric region, the distal femoral shaft region and the proximal tibial shaft region. [ED. NOTE.—His arguments are reasonable, but when length is an important item the use of transverse osteotomy with the interposition of a wedge of bone obtained from nearly exposed sources appears more logical.]

Noting the ease with which the proximal portion of the sciatic nerve, which is well into the sciatic notch, was exposed through a posterior gluteal approach when they were looking for a foreign body, Naffziger and Norcross⁶⁶⁹ have written a paper extolling it as a rational procedure in exposing the posterior aspect of the hip joint and the sciatic nerve before it enters the pelvis. The following advantages are cited: (1) ease of approach; (2) excellent exposure of the region; (3) no severing of important structures, and (4) facilitation of search for foreign bodies in this region.

Taking into account the torsion of the achilles tendon in its nonmuscular portion, White⁶⁷⁰ has directed his fractional subcutaneous transverse tenotomy cuts so as to sever all the fibers at two levels, as one would cut the larger strands of a rope at different levels to sever it. He accounts for the twist by its embryologic development.

As a source of nerve grafts Lam⁶⁷¹ has urged the removal of all nerve trunks from amputated limbs when suitable, in order to avoid the

663. Vere-Hodge, N.: Metallic Internal Fixation of Fractures in Air-Crew Cases. *Brit. M. J.* 2:419-420 (Oct. 2) 1943.

664. Sutherland, R., and Rowe, M. J., Jr.: Metal Hip Belt for Hip Dislocation. *Am. J. Surg.* 62:206-210 (Nov.) 1943.

665. Moore, A. T., and Bohlman, H. R.: Metal Hip Joint: A Case Report. *J. Bone & Joint Surg.* 25:688-92 (July) 1943.

666. Morris, H. H.: Skeletal Traction as a Method of Treatment for Certain Foot Deformities. *Arch. Surg.* 6:736-742 (May) 1943.

667. Burman, M. S.: Plastic Materials in Medicine. *Am. J. Surg.* 62:124-125 (Oct.) 1943.

668. Thompson, V. P.: Telescoping V Osteotomy. *Arch. Surg.* 46:772-779 (May) 1943.

669. Naffziger, H. C., and Norcross, N. C.: Surgical Approach to Lesions of Upper Sciatic Nerve and the Posterior Aspect of the Hip Joint. *Surgery* 12:929-932 (Dec.) 1942.

670. White, J. W.: Torsion of the Achilles Tendon: Its Surgical Significance. *Arch. Surg.* 46:784-787 (May) 1943.

671. Lam, C. R.: Amputated Limbs as Source for Nerve Grafts. *J. A. M. A.* 123:1067 (Dec. 18) 1943.

"begging" of material from pathologists and bereaved persons.

A transverse screw of suitable dimensions through the base of a securely placed Smith-Petersen nail in intertrochanteric fractures is advocated by Thatcher⁶⁷² when lack of extensive comminution allows it. The article is illustrated and describes 22 fractures which have been treated this way successfully. The chief advantages are the ease of instillation and later removal if necessary as well as minimum exposure from my point of view is that complete immobilization is not obtained in the anteroposterior plane. He utilizes a $\frac{3}{16}$ inch (0.5 cm.) pin but he agrees that the screw is better for the purpose except for the fact that it is more difficult to obtain.

Pitkin⁶⁷³ describes a rather complicated surgical technic for bracing the lower part of the back and the sacroiliac joints. He has used it on 53 patients in twelve years. He employs a transverse-tibial graft running from one iliac wing to the other immediately behind the sacrum and just distal to the lumbosacral interspace. Beneath this are placed paraspinous grafts bridging the lumbosacral space and resting on the denuded laminae. He reports 1 operative mortality, and one wonders if the results obtained justify the severity of the procedure. The article would have been much easier to understand if there had been some illustrations or roentgenograms. He reports a high degree of success; all patients returned to their former or equivalent occupations, even the 1 who lost her grafts through infection.

Hatt⁶⁷⁴ reports success in 44 cases of arthrodesis of the knee or ankle by the central graft; 23 cases were instances of arthrodesis of the ankle in children in whom no serious disturbance in growth had occurred. Nothing was mentioned relative to the subastragalar joint, which must have been severely injured when the astragalus driven up through the os calcis and the astragalus and into the tibia. In cases in which involvement is so severe as to require this operation, the persistence of subastragalar motion is of little importance and the amount of damage sustained is therefore of small consequence; hence it may be assumed that arthrodesis occurs in these

cases as well. [ED. NOTE.—In any event, I feel that there is justification for considering this even in a child to be a satisfactory method for arthrodesis of both an ankle and a knee.]

Girard⁶⁷⁵ urges transplanting the hamstring muscles to the symphysis pubis in cases of scoliosis in the presence of pelvic obliquity, if it is certain that they are strong enough to make the operation worth while. The operation also tends to increase the power of the adductor muscle. When the operation is done care must be taken not to injure the obturator nerve, which is the chief nerve supply for the adductor muscle and the small nerve branches.

An excellent discussion has been published by Abbott and Gill⁶⁷⁶ on the approaches to the physal cartilages of the knee and ankle for epiphysal-diaphysal fusion. It should be read by all who are contemplating this procedure.

Townsend and Gilfillan⁶⁷⁷ have devised longitudinally channelized stainless steel plates with oval slots for screw holes. The plate gives it extra strength in addition to the other so that its length may be molded. It is flexible enough to be molded, and screw holes simplify the introduction. The plate can be bent and even cut to any size as desired. [ED. NOTE.—The success of its use will be looked upon with interest.]

The problem of lengthening a limb has been discussed in detail, this time by Brackley⁶⁷⁸, who recites his experiences over many years and reports a formidable series of 10 operations to arrest the growth of the leg which was lengthened below the knee. That shortening of the leg after operations to arrest the growth are now more popular. He states that the disadvantage of the shortening is decreased. [ED. NOTE.—The height is decreased. (Ed. NOTE.—some experience with this)]

675. Girard, P. M.: Paraphysal Transplantation of Origin of Symphysis Pubis. *J. Bone & Joint Surg.* (Jan.) 1943.

676. Abbott, L. C., and Gilfillan, R. L.: Approaches to Epiphysal Cartilages of Ankle Joints. *Arch. Surg.* (Jan.) 1943.

677. Townsend, R. L.: A New Type, California. *Arch. Surg.* (June) 1943.

678. Brackley, A.: Leg Lengthening. *Present Status, California.* (Jan.) 1943.

672. Thatcher, H. H.: Internal Fixation Device for Treatment of Intertrochanteric Fractures of the Femur. *Am. J. Surg.* 60:44-49 (April) 1943.

673. Pitkin, H. C.: Internal Brace for Low Part of the Back. *Arch. Surg.* 46:755-758 (May) 1943.

674. Hatt, R. N.: Central Bone Graft in Joint Arthrodesis. *Arch. Surg.* 46:664-665 (May) 1943.

to call attention to the fact that reducing height of a person increases his general ability, as it lowers his center of gravity. Reduced height is most advantageous in the long in these cases, a majority of which are cases of poliomyelitis, in which increased

general stability is to be desired.] In Brockway's cases in which the leg was lengthened he considered the results extremely good in 65 per cent, good in 22 per cent and poor in 13 per cent. He wisely states that the lengthening procedure is never without some hazard.

NIN. RESEARCH

PREPARED BY A. STEINDLER, M.D., AND STAFF, IOWA CITY

Barr, Lingley and Gall⁶⁷⁹ found the growing epiphysal plate of the albino rat extremely sensitive to roentgen irradiation. They observed the effect of irradiation on one knee joint of albino rats 30, 90 and 160 days old. The resultant changes were studied histologically and roentgenographically. The skin, subcutaneous tissue, ligaments, synovia and articular cartilage showed insignificant transitory changes. On the bone marrow irradiation produced depletion of approximately one half or less of the marrow lular content in the field of irradiation within one to three weeks; the cellular content returned to a normal level in the succeeding two to four weeks.

Doses of 665 to 1,165 r produced moderately severe histologic changes in the epiphysal plate. Higher doses of 1,335 to 1,800 r caused severe injury, as evidenced by disruption of columns of cartilage cells and destruction of chondrocytes. There was no evidence indicating stimulation, and only inconsequentially was there evidence of regeneration of the epiphysal cartilage. Careful measurements of longitudinal growth of the tibia after irradiation showed that all the doses used (665 to 1,800 r) produced retardation of growth and that the retardation varied roughly proportionately to the amount of irradiation administered. The large doses (1,335 to 1,800 r) caused essentially complete arrest of growth of the treated epiphysis.

This investigation was motivated by the possibility of a practical use for the known radiosensitivity of the epiphysal plate in place of the surgical arrest of growth by epiphysiodesis (Phemister).

Brailsford⁶⁸⁰ states that there are variations in the ossification of the bones of the hand, the cause and the frequency of which give rise to difference of opinion. They concur for the most part with the development of the so-called pseudoepiphyses and the true supernumerary epiphyses. The latter are regarded as developments from a separate center of ossification and

the former as bony extensions from the diaphysis into its cartilaginous extremity. The author studied 1,000 roentgenograms of the hand of apparently normal infants up to 3 years of age. 100 roentgenograms of congenital malformations of the hand and 193 of different diseases of the hand. Of the 1,000 roentgenograms of the hands of apparently normal infants 89 showed abnormal ossification of the metacarpal bones; in 83 of these, the abnormal development was of the nature of pseudoepiphyses and in 62 it was located at the proximal extremity of the second metacarpal bone. The impression of the author is that separate additional osseous nuclei may develop in the first and second years of life and fuse before the osseous nuclei of the normal epiphysis appear.

Certain conditions retard the growth of the epiphysis; retarded growth is a characteristic feature of hypothyroidism but does not exist with true supernumerary epiphyses or pseudoepiphyses.

In chondro-osteodystrophy, ossification of each epiphysis proceeds from multiple irregular ossific nuclei, but there is no true epiphysis or pseudoepiphysis. Roentgenograms of congenital deformities did not show either true epiphyses or pseudoepiphyses. Craniocleidodysostosis is regarded as a condition in which defective ossification occurs only in those bones which are laid down in membrane, but the author found modifications of the bones of the hand also. He reports the presence of additional epiphyses to the middle and proximal phalanges and dysostosis which often affects only the long bones of the hand and feet. In cases of arachnodactyly true supernumerary epiphyses are seen in the phalanges and metacarpal bones of the long, slender fingers. Extra epiphyses may be seen also in cases of multiple chondromas and achondroplasia.

An attempt was made by Duckworth and Warnock⁶⁸¹ to construct a composite picture of the behavior of calcium and magnesium in man during his development. Requirements of cal-

679. Barr, J. S.; Lingley, J. R., and Gall, E. A.: Effect of Roentgen Irradiation on Epiphysal Growth: Experimental Studies upon Albino Rat, *Am. J. Roentgenol.* 49:104-115 (Jan.) 1943.

680. Brailsford, J. F.: Variations in Ossification of Bones of Hand, *J. Anat.* 77:170-175 (Jan.) 1943.

681. Duckworth, J., and Warnock, G. M.: Magnesium Requirements of Man in Relation to Calcium Requirements, with Observations on Adequacy of Diets in Common Use, *Nutrition Abstr. & Rev.* 12:167-183 (Oct.) 1942.

cium were estimated from data on calcium metabolism for normal children in relation to independent studies of skeletal growth.

An analysis of the data afforded by dietary surveys suggests that the lower income groups, representing 30 per cent of the population, have habitual intakes of magnesium that are either borderline or deficient as judged by requirements; these estimates provide, as far as can be seen, no margin of safety.

Duncan and Blalock⁶⁸² performed experiments in which a mechanical press was applied to an extremity for an extended period (fifteen hours). The animals died even though plasma was given intravenously in an amount equal to that lost locally. The same experiment with the pressure applied for only five hours did not always cause death. Hence it is felt that ischemia and anemia over the extended time were responsible for the severity of the shock.

The authors then studied the effects of applying a tourniquet to an extremity after injury to the soft tissues.

Method: A leg of each of 10 large animals was traumatized by blows from a hammer. Then a tourniquet was applied proximal to the damaged area. A leg of each of 10 control animals was also traumatized, but a tourniquet was not used. Control animals were given plasma two hours following the traumatization; test animals were given plasma in five hours, just at the time the tourniquet was removed. Five per cent of the body weight was the amount of plasma given to the control animals and 5 of the test animals. The other 5 test animals were given 9 per cent of their body weight.

Results: Of the control animals, 8 recovered and 2 died. One died in ninety hours; autopsy revealed pneumonia and an abscess of the thigh. The other died on the twenty-fifth day and also had an abscess.

All 10 test animals died within three to thirty-six hours, the average being about fourteen hours.

	Control Group	Test Group
Pulse	Slight rise	Accelerated
Blood pressure	Little alteration	Gradual fall
Plasma creatine	Little alteration	Elevated
Nonprotein nitrogen	Little alteration	Elevated
Urine	Slight reddish discoloration and few erythrocytes	Darker in color, moderate number of erythrocytes and granular casts
Hematocrit reading	Little change	Decline

682. Duncan, G. W., and Blalock, A.: Effects of Application of Tourniquet on General Response to Gross Trauma to an Extremity, *Surgery* 13:401-405 (March) 1943.

The authors conclude that the application of a tourniquet to an injured extremity greatly lessens the chances of survival of the animal.

Fell and Hanselman⁶⁸³ carried out experiments which showed that severe freezing of a dog's extremity results in extensive local necrosis, clinical shock and death in most cases.

Ten dogs were anesthetized and the hindlimb immersed up to the upper third of the thigh in a mixture of solid carbon dioxide and 95 per cent alcohol at -55°C . for twenty minutes. Five dogs received no form of treatment and were allowed to thaw out at room temperature. The other 5 dogs had two or three layers of sheet wadding wrapped around the extremity, over which a plaster encasement was applied above the frozen line.

All 5 untreated dogs acquired clinical shock with 4 dying in thirteen hours. All of the treated dogs lived, and the maximum increase in hematocrit reading was only about one-half as great as for the untreated group. One treated dog had its limb amputated in forty-eight hours and recovered. Necrotic limbs developed in the other 4; 2 had their limbs amputated eight and eleven days following freezing and made uneventful recoveries; 1 died nine days after freezing from a second degree infection; the other dog died of peritonitis following disarticulation fourteen days after freezing.

They conclude that immediate application of a smooth plaster pressure bandage saved the dogs from shock and death after the hindlimb had been frozen.

Gardner⁶⁸⁴ determined the "breaking strength" of the femurs of 241 mice which had received estrogen or estradiol benzoate plus testosterone propionate under uniform conditions: also determined was the "breaking strength" of the femurs of 162 untreated mice of the same stock. In the untreated mice, the femurs declined in strength as the mice advanced in age and the bones of the females were stronger than those of the males. The most radiopaque femurs showed the greatest resistance to fracture.

In the estrogen-treated mice the breaking strength of the femurs was much greater than in the control animals of the same age. The estrogen-treated male mice had stronger femurs than the estrogen-treated female mice. The

683. Fell, E. H., and Hanselman, R.: Prevention of Shock and Death by Immediate Application of Pressure Dressing to Severely Frozen Limbs of Dogs: Experimental Study, *Ann. Surg.* 117:686-691 (May) 1943.

684. Gardner, W. U.: Influence of Sex and Hormones on Breaking Strength of Bones of Mice, *Endocrinology* 32:149-160 (Feb.) 1943.

ultaneous injection of testosterone propionate and estrogen prevented the increase in strength observed in mice given estrogen alone. The bones of the female mice given testosterone propionate were much weaker than the bones of the untreated control mice of the same age group. Reed and Reed⁶⁸⁵ begin an article on antirachitic healing by briefly discussing the equipment, the methods and the experimental material. When examined by roentgen diffraction technique, the cortices of the tibias of albino rats showed characteristic preferred orientation on the long axis of the bones. The identity of bone salts with apatite was confirmed by the finding of nearly identical powder diffractograms of bone and apatite. It is the authors' opinion that disorientation in rickets bears no direct relation to the ability of bones to resist mechanical stress, and bones of rachitic rats may be restored, but disorientation is not repaired completely in two hundred and seventy-five days with an antirachitic diet.

The authors state that they have not been able to determine as yet whether disorientation has any physiologic significance other than as an indicator of a type of metabolic disturbance.

Schiller, Struck and Reed⁶⁸⁶ give a brief discussion of experimental methods and describe an apparatus for applying a quantitative breaking test to the bones of rats. The experiments involved 267 animals, and the results indicated that the tibias of rats that had been rachitic and then healed, when compared with those of litter-mate control rats, showed significant differences in resistance to lateral breaking stress in two of nine series.

Annersten⁶⁸⁷ goes further into the chemistry of bone, showing by formulas the chemical process by which the reactions occur. He stresses the importance of p_H of the blood, especially at the site of fracture, and the enzyme contained in tissues by which bone cells are differentiated from mesenchymal tissues. He feels that much work is yet to be done to explain fully all the chemical processes of healing of bone.

Bell and Cuthbertson⁶⁸⁸ ran a series of experiments on white rats. They were fed an adequate diet, and certain hormones were given with the diet.

Extract of the anterior lobe of the pituitary gland produced bigger and proportionately stronger bones than those of control animals which had received injections of extract of thymus, but there was no alteration in the breaking stress.

Estradiol dipropionate produced heavier and stronger bones but no change in breaking stress.

The femurs of rats treated with parathyroid extract were longer and heavier than those of either rats treated with estradiol or control rats. The breaking stress remained unchanged.

Thyroid produced a greater change in soft tissue than in mineral matter. The quality of bone remained the same.

Bruce and Kassner⁶⁸⁹ used various bones to compute values of bone ash. The percentage of ash in dry fat-free humerus was chosen as the basal value, and the results were evaluated irrespective of sex and the dose of vitamin D given.

When low calcification in rats, as measured by ash content of the humerus, is due to shortage of vitamin D, the femur shows an even lower calcification. When it is due to deficiency of either calcium or phosphorus without a shortage of vitamin D, no difference in calcification is observed. In the femur both the relatively large metaphysis and the extremely low calcification of this part make the ash content of the whole bone lower than that of the humerus when vitamin D is lacking. Sex does not make any difference in the humerus or the femur.

Clavert⁶⁹⁰ credits Zondick (1937), Landaner, Gardner and Pfeiffer (1939), in experiments on the pigeon and chicken, and Bensit, Messerschmidt and Grangaud (1941), in experiments on the duck, with having found by regular injections of estradiol dipropionate an estrogenic action similar to that found in female birds. He repeated the experiment on 17 male pigeons and 1 castrated female pigeon.

685. Reed, C. I., and Reed, B. P.: Attempted Correlation of Mechanical Properties of Bone with Antirachitic Healing and with Molecular Structure as Determined by X-Ray Diffraction Technique, *Am. J. Physiol.* **138**:34-41 (Dec.) 1942.

686. Schiller, A. A.; Struck, H. C., and Reed, C. I.: Influence of Rickets and of Healing of Rickets on Mechanical Properties of Tibiae of Rats, *Am. J. Physiol.* **138**:27-33 (Dec.) 1942.

687. Annersten, S.: Alkalinization in Fracture Callus, *Arch. f. klin. Chir.* **203**:122-136, 1942.

688. Bell, G. H., and Cuthbertson, D. P.: Effect of Various Hormones on Chemical and Physical Properties of Bone, *J. Endocrinol.* **33**:302-309 (Aug.) 1943.

689. Bruce, H. M., and Kassner, E. W.: Difference in Calcification Between Humerus and Femur of Young Rats Receiving High Calcium, Low Calcium, and Stock Diets, *J. Biochem.* **37**:105-109 (April) 1943.

690. Clavert, J.: Osteogenetic Action of Estradiol Dipropionate (Estrogen) in Pigeons, *Compt. rend. Soc. de Biol.* **136**:512-515, 1942.

The daily injection of estradiol during several weeks excites in many bones of the male pigeon intense osteogenesis, which is greater than that in females. It reacts by osteogenesis of a medullary type. Springing always from a preexisting substratum, the bony bridges invade the medullary cavity and then condensate by apposition of bony layers. The medulla preserves its activity. Fat tissue disappears.

Foshee⁶⁹¹ presents a study of regenerative power of fascia lata. Kleinschmidt has demonstrated that normal fascia lata contains three distinct layers, each within its own sheath and the three within a common denser sheath. The middle layer is strongest and runs longitudinally. The inner and outer layers are weaker, and their fibers run transversely at an angle of 90 degrees to those of the middle layer.

Fascia lata regenerates to fill defects left when tissue is removed. In thin, muscular persons the margins of fascia lata approximate to close the vent by rapid and thick formation of fibrous tissue, which is in all probability derived from the inner and outer layers. In obese persons the margins of fascia retract farther and for a short time permit some formation of muscle through the vent, but soon the defect is filled by new fascia lata one-half the thickness of the old fascia lata. This is thought to be the regeneration of the outer and inner layers of the true fascia lata.

When every iota of fascia lata is removed, new fascia lata of from one half to two thirds of the thickness and tensile strength of the previous tissue regenerates to cover the whole area normally covered by fascia lata, and it may well be used again for sutures and transplants as well as for the true purpose of the tissue, that of making a sleeve for muscles and preventing herniation.

Katzenstein, Mylon and Winternitz⁶⁹² undertook experiments to find out the effect of injection of thoracic duct fluid collected promptly after the release of tourniquets which had been applied to the hindlegs of dogs. They found that the thoracic duct fluid becomes blood stained after release of the tourniquets and that when this fluid is injected intravenously its effect on blood pressure is variable; but in some cases 7 cc. of fluid may produce a severe and pro-

tracted fall in blood pressure, which may cause death of the animal.

The authors also observed that change in blood pressure and other signs of shock follow nothing more than anesthesia induced by pentobarbital sodium. In experimental cases in which narcosis was controlled to avoid depression, injection of thoracic duct fluid in normal dogs had no significant effect while in fall in blood pressure followed in 50 per cent of the animals which received injection of thoracic duct fluid of animals shocked by the tourniquet method.

Segaloff and Cahill⁶⁹³ studied the change in the bones in mice treated with estrogen and fed a diet deficient in vitamin D. They based their experiments on previous investigations made by other authors, who found extensive proliferation of endosteal bone in the femurs of mice treated with estrogen and maintained on adequate diet. The estrogenic agent administered in this case was estradiol dipropionate, and the duration of treatment was twelve weeks.

Obliteration of the marrow cavity of the femur by endosteal bone and some resorption of bone were observed in a strain of mice fed on commercial stock diets and treated with estrogen. Mice of the same strain treated with estrogen and fed a diet deficient in vitamin D supplemented with viosterol showed typical changes in the femur. This result was also obtained in animals fed the same diet unsupplemented with vitamin D. It is concluded, then, that deficiency of vitamin D did not play a major role in the mechanism of deposition of endosteal bone in the femurs of mice treated with estrogen.

Torda⁶⁹⁴ investigated whether or not the presence of androgens, estrogens and some of the hormones of the hypophysis modified muscular contraction produced by known chemical agents. Both the sensitivity of striated muscle to acetylcholine and potassium activity of choline esterase of brain tissue were investigated in the presence of the previously mentioned hormones. It was found that the sensitivity of the muscle to acetylcholine is somewhat potentiated by chorionic gonadotropin, estrone and estradiol, the corpus luteum hormone, testosterone propionate and the pressor and antidiuretic hormone of the posterior pituitary.

691. Foshee, J. C.: Fascia Lata Regeneration: Preliminary Report, *Surgery* 14:554-569 (Oct.) 1943.

692. Katzenstein, R.; Mylon, E., and Winternitz, M. C.: Toxicity of Thoracic Duct Fluid After Release of Tourniquets Applied to Hind Legs of Dogs for Production of Shock, *Am. J. Physiol.* 139:307-312 (June) 1943.

693. Segaloff, A., and Cahill, W. M.: Enzyme Activity and Bone Deposition in Femurs of Vitamin D-Deficient Mice Treated with Estrogen, *Proc. Soc. Exper. Biol. & Med.* 54:162-163 (Oct.) 1943.

694. Torda, C.: Effect of Hormones on Contractility of Striated Muscle and on Choline Esterase Activity, *Proc. Soc. Exper. Biol. & Med.* 53:121-125 (June) 1943.

be of the hypophysis but not by the oxytocic principle of the posterior lobe of the hypophysis. The activity of choline esterase is somewhat increased by chorionic gonadotropin, estrone suspension, progesterone, testosterone propionate and pitressin but not by pitocin.

The sensitivity of the muscle to potassium is potentiated by chorionic gonadotropin, estrone suspension, estradiol, estrone, progestin, progestoral (anhydrohydroxyprogesterone), testosterone propionate, desoxycorticosterone, cholesterol and pitressin but not by pitocin.

A correlation between the threshold of excitability of the effector cells and the presence of these substances was suggested.

Warkany and Schraffenberger⁶⁹⁵ describe the appearance of congenital malformations in the offspring of female rats fed a deficient diet composed of yellow cornmeal 76 per cent, wheat 20 per cent, chemically pure calcium carbonate 3 per cent and chemically pure sodium chloride 1 per cent. Sixty international units of vitamin D as viosterol was administered to each female by pipet every tenth day. The malformations could be prevented in the offspring when the maternal diet was supplemented by 1 per cent dried pig liver. The authors used in their experiments a purified diet which contained vitamin B complex but not riboflavin. They obtained congenital malformations in the offspring that were anatomically identical with those obtained with the other diet. The malformations consisted in shortness of the mandible, fibula, radius and ulna, fusion of the ribs, center of ossification of the sternum, syndactylism, brachydactylism and cleft palate.

Whicher and Watson⁶⁹⁶ found that certain hormonal preparations when injected into albino rats apparently produce changes in the phosphatase content of the femur. It was observed that repeated doses of small amounts of parathyroid extract cause a temporary increase of the phosphatase content of the diaphysis without alteration of this enzyme in the epiphysis. Large single doses of the extract cause an increase followed by a decrease of the phosphatase content of the diaphysis while there is only a decrease in the epiphysis. The injection of adrenal cortical extract is followed by a reduc-

tion of the phosphatase content in both the diaphysis and the epiphysis. The authors observed in their experiments the effects of the hormones derived from the anterior pituitary gland and concluded that both the thyrotropic hormone and the gonadotropic factor, injected subcutaneously, caused an increase of the phosphatase content of the diaphysis and the epiphysis. The results obtained with pituitary extract purported to contain the growth-stimulating principle were not consistent. In some experiments they produced an increase, in others a decrease and in others no changes whatsoever. Insulin did not cause any modification in the phosphatase content of the bones of the rats, and potassium iodide produced an increase of the phosphatase content of the femurs of albino rats.

Foa⁶⁹⁷ reviews the history of studies on innervation of bone marrow, from the first postulation of such in 1700 to the present recent contribution by Rossi.

Rossi described the main nerve trunks which follow the arteries of the bone marrow, both at the center and at the periphery, in the medullary canal. From these trunks are derived loose nets in the endothelial walls of the venous sinuses. Myelinated and unmyelinated fibers are present in about the same number. He also recognized fibers destined for cellular elements of the bone marrow and of the bone itself. These fibers do not follow the blood vessels. Terminal nerve endings were demonstrated to be of several types. There appeared to be a crowding of blood-forming elements around these terminations. The majority of these fibers are myelinated, while the unmyelinated fibers are in close contact with the blood vessels, especially the muscular coat and the endothelium.

Thus, according to Rossi there are two types of nerve fibers of the bone marrow: (a) the unmyelinated fibers, which are in close relationship to the muscular coat and endothelium of the blood vessels; (b) the myelinated fibers, which seem to be closely related to the blood-forming cells.

Gomori⁶⁹⁸ discusses the relationship between the activity of phosphatase and calcification under normal and pathologic conditions, as shown by a new microtechnical method for simultaneous visualization of preformed deposits

695. Warkany, J., and Schraffenberger, E.: Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency: Effects of Purified Diet Lacking Riboflavin, *Proc. Soc. Exper. Biol. & Med.* **51**:92-94 (Oct.) 1943.

696. Whicher, C. H., and Watson, E. M.: Effects of Thyrotropic Hormone, Gonadotropic Factor, Pituitary Growth Substance and Insulin upon Phosphatase Content of Rat Femurs, *Endocrinology* **33**:83-86 (Aug.) 1943.

697. Foa, P. P.: Studies on Innervation of Bone Marrow: Anatomy, *Univ. Hosp. Bull., Ann Arbor* **9**: 9-10 (Feb.) 1943.

698. Gomori, G.: Calcification and Phosphatase, *Am. J. Path.* **19**:197-209 (March) 1943.

of calcium salts and of sites of phosphatase activity.

Since calcium salts are removed and phosphatase destroyed by decalcification, all material studied was embedded and cut without decalcification. Thus tissues too hard to be sectioned were not studied. The tissue was stained by methods for demonstration of phosphatase, devised for the purpose of simultaneous visualization of preformed deposits of calcium salts and of sites of phosphatase activity.

Observations on normal material and on pathologic material were made. Of the latter, bone tumors tuberculosis and calcification in hyaline cartilage were studied with the phosphatase-staining technic.

Conclusions were that calcification of living or recently necrosed tissues seems invariably to involve activity of phosphatase. On the other hand, calcification of hyaline connective tissue occurs without any action of phosphatase. Acid phosphatase plays no role in calcification.

Henry⁶⁹⁹ describes a method of exposing the arched proximal segment of the anterior tibial

vessels, which he feels is important because the fact that most surgeons are unprepared to stop bleeding from the arch by direct exposure. Other methods used for this purpose, such as reflection of the fibula or direct pressure with a tampon, seem unsatisfactory because of extensiveness of the procedure or the danger to residual blood supply.

With the patient in the prone position, the arch of the tibial vessels is exposed through a posterior and medial incision which extends down between the two heads of the gastrocnemius muscle. Since the arch segment is fast in front by soft tissue, mobilization is possible until the arch is mobilized in the anterior compartment of the leg. To accomplish this an anterior incision is made between the fibula head and the tibia, extending deep between the extensor digitorum longus and tibialis anterior muscles. Thus after the arch has been freed anteriorly the entire segment can be brought into view in the posterior part of the wound.

699. Henry, A. K.: Exposure of Arched Segment of Anterior Tibial Vessels, *Lancet* 1:141-142 (Jan. 3) 1943.

PREFACE

In the preparation of this review of orthopedic surgery for 1943 the titles of 1,252 articles of orthopedic interest were selected from the *Quarterly Cumulative Index Medicus* for 1943. The number of articles reviewed and presented in this year's "Progress" is 699. This is a smaller number of articles than that selected for previous years. The smaller number of articles is due to the decrease in the volume of medical literature since the war commenced. As in the past three years, each editor has selected the articles for his section which he thinks represent the most progress and have the greatest scientific interest. The chairman or Dr. R. B. Raney of the editorial board has reviewed the material prepared for each section and has made certain additions and changes which seemed indicated to standardize to improve the publication as a whole.

On account of the difficulties under which many of the editors have been working, the reviews of some of the sections have been slower in being returned to the chairman of the editorial board, and, as was true last year, it was found impossible to send the whole "Progress" to the *ARCHIVES* at one time. This has necessitated a slight change in the order of the sections for publication. The preface could not be written until all sections had been submitted. Unfortunately, the section on "Conditions Involving the Hip Joint" was not received in time to be included in the "Progress" for 1943. The articles

selected for review in this section will be included in the "Progress" for 1944. In spite of the difficulties encountered in getting reprints, it is believed that the quality of the reviews is up to standard and the publication will prove as valuable to its readers as the "Progress" of previous years.

The members of the editorial board wish to thank again those physicians not members of the American Academy of Orthopaedic Surgeons who have rendered such valuable assistance in the preparation of the material for the various sections. Special thanks are rendered to Dr. Harold H. Kuhn for editing the section on "Conditions Involving the Lower Part of the Back."

The following physicians acted as assistants to members of the editorial board:

Dr. Ghormley: Dr. H. H. Young, Dr. W. H. Bickel, Dr. T. R. Lipscomb, Dr. R. D. Mussey Jr., Dr. J. M. Regan and Dr. F. Padilla.

Dr. Colonna: Dr. David King and Dr. Thomas Gucker.

Dr. Steindler: Dr. A. C. M. Bitar, Dr. E. A. Cobb, Dr. J. E. Fuchs, Dr. A. J. Langan, Dr. James L. LeNoir, Dr. Ignacio Pons and Dr. Jose Puig.

Dr. Meyerding: Dr. J. M. Regan, Dr. Mussey Jr., Dr. J. F. Stotler, Dr. J. J. Hinchey.

Dr. J. H. Remington, Dr. Federico Padilla and Dr. A. R. Pils.

Dr. Hauser: Dr. Robert P. Montgomery.

Both style and editorial comments have again been left to the discretion of the editors, except for a few changes made by the chairman of the editorial board or by Dr. R. B. Raney. It should

be stated again, however, as in the preface of the "Progress" of previous years: "If the reader or author of any article does not agree with the editorial comment, the editorial board hopes that he will think of the remark as only one man's impression and as in no way representing the opinion of the entire editorial board."

THE EDITORIAL BOARD OF THE
"PROGRESS OF ORTHOPEDIC SURGERY"

LENOX D. BAKER, M.D., Chairman

GLENN BARBER, M.D.

WALTER P. BLOUNT, M.D.

FREMONT A. CHANDLER, M.D.

JOHN R. COBB, M.D.

PAUL C. COLONNA, M.D.

H. EARLE CONWELL, M.D.

JOHN J. FAHEY, M.D.

RALPH K. GHORMLEY, M.D.

A. BRUCE GILL, M.D.

PAUL HARMON, M.D.

EMIL D. HAUSER, M.D.

HERMAN F. JOHNSON, M.D.

J. HIRAM KITE, M.D.

JOHN G. KUHN, M.D.

HENRY W. MEYERDING, M.D.

D. H. O'DONOGHUE, M.D.

WINTHROP M. PHELPS, M.D.

R. BEVERLEY RANEY, M.D.

JESSE I. SLOAT, COLONEL, M.C., U.S.A.

ALAN D. SMITH, M.D.

J. SPENCER SPEED, M.D.

ARTHUR STEINDLER, M.D.

LORING T. SWAIM, M.D.

J. WARREN WHITE, M.D.

A REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES

FRANK HINMAN, M.D.
SAN FRANCISCO

ALEXANDER VON LICHTENBERG, M.D.
MEXICO, D. F., MEXICO

ALEXANDER B. HEPLER, M.D.
SEATTLE

ROBERT GUTIÉRREZ, M.D.
NEW YORK

COMMANDER GERSHOM J. THOMPSON (MC), U.S.N.R.

EDWARD N. COOK, M.D.
ROCHESTER, MINN.

EGON WILDBOLZ, M.D.
BERNE, SWITZERLAND
AND

VINCENT J. O'CONOR, M.D.
CHICAGO

KIDNEYS

Anomalies.—Nation¹ states that renal agenesis implies the complete absence of renal tissue. The renal anlage develops in most cases, even in the absence of a ureter, but is usually absorbed unless normal fusion with the ureter occurs.

Three cases of bilateral renal agenesis from a series of 27,000 autopsies are reported. This makes the total number of reported cases 124. Besides the 3 cases described in this paper, only cases in which the abnormality has been limited to the mesonephric and metanephric systems have been reported.

Twenty-seven cases of unilateral renal agenesis are cited. Fourteen of these were encountered in a series of 27,000 autopsies at the Los Angeles County Hospital, a ratio of 1 to 1,929. Five cases were found in a series of 1,831 autopsies at the Huntington Memorial Hospital, an incidence of 1 in 366 autopsies. The ratio for the combined series is 1 case to 1,517 autopsies. Nation also reports 6 clinical cases.

There were 18 (67 per cent) males and 9 (33 per cent) females. In the series of autopsies, unilateral renal agenesis was 20 per cent more

common in males than in females (figure corrected for the fact that 60 per cent of all of the autopsies were performed on males).

In the series of clinical cases, all the patients were under 49 years of age. The right and the left kidney were absent with equal frequency. The adrenal gland was present in 17 cases and was recorded as absent in none. In 21 cases (77 per cent) the ureter and half of the trigone were absent. The solitary kidney was always enlarged unless shrunken by disease. In 58 per cent of the cases in which autopsy was performed there were congenital abnormalities of the single kidney. In 22 per cent of the cases the single kidney was diseased; in 6 cases renal failure was the cause of death (congenital inadequacy of the single kidney in 3 cases and renal disease in 3 cases).

Four (44 per cent) of the women had developmental defects of the genital organs. Two (11 per cent) of the men had such defects. Only 3 (21 per cent) of the patients on whom autopsy was performed had hypertension.

There is no reliable clinical sign which guarantees the differentiation of renal agenesis and renal aplasia.

Culp² states that secondary lesions sometimes develop in horseshoe kidney and may be of any of the pathologic types which affect a nonfused kidney. A horseshoe kidney with secondary pathologic involvement represents the most com-

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

1. Nation, E. F.: Renal Agenesis: A Study of Thirty Cases, Surg., Gynec. & Obst. 79:175-181 (Aug.) 1944.

2. Culp, O. S.: Treatment of Horseshoe Kidneys. Ann. Surg. 119:777-787 (May) 1944.

on type of horseshoe kidney which is recognized initially, and the symptoms usually are due to a secondary pathologic process. Secondary disease of major significance should be treated by eminephrectomy. Less radical procedures which reserve both halves of the kidney (for example, pyelolithotomy) should be accompanied with symphysiotomy and nephropexy on the side of the kidney because of the danger of remaining symptoms attributable to the fusion alone.

A small, but distinct, group of horseshoe kidneys without a secondary pathologic process presents vague symptoms in the abdomen or back, which may be mistaken for indications of gastrointestinal disorder or a pathologic condition in some other system. Apparently the symptoms of the "horseshoe kidney syndrome" are produced by pressure on adjoining nerves by the isthmus of fusion or by the ectopic renal masses. Relief is obtained by symphysiotomy and nephropexy. In a few cases of this syndrome it may be necessary to perform a nephropexy on the opposite side also before complete relief is obtained.

For all surgical procedures on horseshoe kidney the conventional extraperitoneal-lumbar approach is satisfactory and is the one of choice.

Culp adds another case to the small group in which treatment with symphysiotomy and bilateral nephropexy was successful. Pyelolithotomy also was performed in this case. Recurrent calculi were recognized early and were dissolved with "solution G," a solution of citric acid, magnesium oxide and sodium carbonate of pH 4, after irrigation of the renal pelves through indwelling ureteral catheters. The patient has been followed for seven months, with no further recurrence of calculi or symptoms.

Horseshoe kidney is usually the result of union of the lower poles and seldom of union of the upper poles, the latter type being often accompanied by other anomalies, such as horseshoe adrenals, diaphragmatic hernia and spina bifida. Of great importance is the anomalous blood supply of this double kidney. The arteries usually enter the kidney posterior to the pelvis and vary in number from four to six, with one or two entering the symphysis. The ureters cross in front of the symphysis, and anomalous, or aberrant, arteries are the rule, often taking their origin from the arteries of adjacent structures.

Tumors.—Wilms's Tumor: Eliason and Stevens³ report a case of Wilms's tumor (embryonal carcinosarcoma of the kidney) in a horseshoe kid-

ney. The patient, a child of 6 years, had a large abdominal tumor and a high fever. An intravenous urogram showed a horseshoe kidney. There was a large, soft tissue mass containing calcium in the left upper quadrant of the abdomen, above the renal area. A transperitoneal incision was made, and a tumor was observed arising from the upper pole of the left segment of a horseshoe kidney. The lesion, including the entire left renal component, was removed without difficulty, the horseshoe kidney being divided at its symphysis. The pathologic diagnosis was embryonal sarcoma of the kidney.

In regard to the treatment of Wilms's tumor there are two schools of thought. The older school advocates preoperative irradiation over the growth, with two objects: (1) to reduce the size of the local mass, so that it will be technically easier to remove, and (2) to kill off the more malignant, radiosensitive cells in the tumor and thus prevent their escape into the blood stream during the operative manipulation.

Ladd, who has had the greatest personal experience with the problem at the present time, recommends removal of the mass as soon as it is discovered, the transperitoneal approach being used, with ligation of the renal vessels before manipulation of the mass. He is convinced that roentgen ray therapy has been too widely employed, without consideration of the end results. Perhaps the most convincing arguments in favor of his thesis are the reputed cures. The few apparently cured patients referred to in the literature received no preoperative irradiation. During the last eight years Ladd has removed 22 Wilms tumors, with no operative mortality, thus refuting the statement that preoperative irradiation is necessary to insure a low operative mortality. Listed in his series as probably cured of renal embryoma are 14 of a series of 56 patients, who were alive and well from two to twenty-one years after operation. Only 1 of the 14 patients had preoperative irradiation.

Bothe, in an analysis of 44 cases from the literature, observed that recurrences and metastases were reported in some instances ten years after removal of the primary growth. With this possibility in mind, he states that the skeptical analyst would accept but 8 of the 44 cases as instances of cure. It is important to note that in these 8 cases neither preoperative nor postoperative irradiation was carried out. He adds 7 personal cases in which treatment without previous irradiation was employed. Finally, he states that he agrees with Ladd that immediate removal of these mixed tumors, or embryomas, gives a better chance of cure than do irradiation and delayed nephrectomy.

3. Eliason, E. L., and Stevens, L. W.: Wilms' Tumor in a Horseshoe Kidney, *Ann. Surg.* **110**:788-790 (May) 1944.

Gutiérrez speaks of the "horseshoe kidney disease" and states that in horseshoe kidney, nephritis, pyelitis, pyonephrosis or stone almost invariably develops sooner or later, with resultant death. The horseshoe kidney is not immune to hypernephroma or papillary carcinoma but rarely produces the Wilms lesion. Eliason and Stevens could not find the report of a single case of Wilms tumor in a horseshoe kidney.

Adenoma: Higgins⁴ reports 6 cases in which a large benign adenoma of the kidney was removed surgically, and he reviews a collected series of 29 cases of large adenoma of the kidney, with surgical intervention in 26 instances. As a papillary adenoma of the kidney enlarges, structural changes may occur and produce a tumor which is histologically similar to hypernephroma. From available data and histologic study it may be assumed that in some instances malignant epithelial tumors of the kidney develop from papillary adenomas. A large adenoma of the kidney which produces symptoms and requires surgical removal is rare.

Other Malignant Growths: Bandler and Roen⁵ state that the most common tumor of the urogenital tract in children is Wilms's tumor of the kidney. Diagnosis can be made in most instances by urographic examination. Preoperative and postoperative roentgen ray therapy should be given. The transperitoneal approach for removal of the kidney should be employed. Less frequent are tumors of the adrenal gland, bladder, prostate and testis, but the possibility of their existence, even in young persons, must be emphasized. A thorough search made for signs of these highly malignant growths. Early diagnosis of malignant disease of the genitourinary tract in children is necessary for successful therapy. In all cases combined treatment with roentgen irradiation and operation should be resorted to; roentgen ray therapy should not be employed alone except in cases in which widespread metastases are present.

Calculi.—Bugbee⁶ reports 2 cases in which nephrolithotomy for recurrent branching calculi was performed by a new technic. Briefly, the procedure was as follows: An incision was made posterior to and below the scar of the primary operation. Because the line of this incision was devoid of scar tissue and because it was well posterior to the reflection of the peritoneum, the

new incision could be readily carried through the various layers of the abdominal muscles and the lumbodorsal fascia down to the perirenal fascia. The upper flap was freed to the level of the last rib, the scar tissue of the former operation being elevated with this flap. In the 2 cases cited, the kidney was placed high up under the last rib, where such kidneys usually are when firmly adherent, especially when they have previously been drained by nephrostomy. The twelfth rib was resected, and the branching calculus in the pelvis and lower calix could then be easily palpated through the perirenal fascia and the thinned-out renal parenchyma without separating the renal fascia from the adherent kidney. One incision was made extending through the perirenal fascia and the renal parenchyma on a line approximately just posterior to the convex border of the kidney and was deepened until the calculus was freely exposed, lying in the pelvis and the lower calix. The calculus in each instance was readily removed and the kidney drained by a tube placed in the lower calix. The renal incision was then closed with mattress sutures, which were passed through the perirenal fascia and thinned-out renal parenchyma on each side of the incision. The fascia prevented these sutures from tearing through the parenchyma and offered excellent resistance when traction was applied in tying the sutures, so that the bleeding was completely controlled. The fibrous tissue in the abdominal wall and the scar of the first operation were then excised, and the abdominal wound was closed in layers about the drainage tube. In both these cases there was no postoperative bleeding, the drainage tube was removed in from seven to ten days and the wound had completely closed in two weeks.

De la Peña and de la Peña⁷ report a case which illustrates the time necessary for formation of a large staghorn renal calculus. The patient, a woman aged 37, stated that during the past three years she had suffered periodically from colicky pain which was referred to the left renal area. She stated that she had been on elsewhere a year before; according to history, drainage of the left kidney had been done. The tube was allowed to remain months, and the wound closed spontaneously after its removal. A roentgenogram of the urinary tract revealed two small stones in the renal area. There was no evidence of any in the right renal area. A month later she was seized with severe colic referable to the

4. Higgins, C. C.: Adenoma of the Kidney: Report of Six Cases, *Am. J. Surg.* 65:3-14 (July) 1944.

5. Bandler, C. G., and Roen, P. R.: Tumors of the Urogenital Tract in the Young, *Am. J. Surg.* 65:306-314 (Sept.) 1944.

6. Bugbee, H.: Nephrolithotomy for Recurrent Branching Calculi, *J. Urol.* 52:99-107 (Aug.) 1944.

7. de la Peña, A., and de la Peña, E.: Case Report Illustrating Brief Period of Time Necessary for Formation of Large Stag-Horn Renal Calculus, *J. Urol.* 52:108 (Aug.) 1944.

lea on the right side, with fever. A plain roentgenogram made thirty-eight days after the previous one showed a large staghorn calculus filling the right renal pelvis. The patient refused to undergo operation.

Ptosis.—Bandler, Pinck and Roen⁸ reviewed 5 cases of nephroptosis deemed suitable for surgical suspension. They believe that operation solely for the correction of excessive renal mobility in the absence of symptoms or stasis is not warranted. Nephropexy alone, without correction of concomitant renal or ureteropelvic lesions, is doomed to failure. A properly performed nephropexy not only demands suspension in a high position but requires fixation, so that the proper renal axis is obtained. This is obviously necessary for adequate drainage of the renal pelvis.

There are specific indications for fixation of the kidney. It must be definitely established that symptoms are referable to the urinary tract. Investigation of nonurinary disturbances, such as gastrointestinal distress, must be complete before such symptoms are attributed to the abnormally mobile kidney. Excessive renal mobility must be demonstrated by urographic examination with the patient in both the erect and the recumbent posture. Simulation of pain by overdilatation of the pelvis on the affected side with retrograde catheterization is a helpful, but by no means essential, diagnostic criterion. Renal displacement, despite the absence of evidence of constant obstruction to urinary outflow, may require fixation of the kidney because of frequent and severe pain, such as occurs in repeated Dietl's crises. When infection is present and yet no stasis can be demonstrated, conservative measures directed toward elimination of the infection should be attempted first. On the other hand, the observation of definite stasis and obstruction to the urinary outflow, in addition to the ptosis, would appear to make the surgical procedure even more imperative.

Trauma.—Adams⁹ analyzed 7 cases of severely ruptured kidney. In 6 cases early operation was performed. In 1 case there was associated rupture of the spleen. There were no deaths. The importance of early operation is stressed, but only after primary shock from trauma to nerve plexuses about the renal pedicle is controlled and before secondary shock from hemorrhage occurs. Preoperative evidence of urinary extravasation

can be demonstrated satisfactorily by intravenous urograms. Retrograde urographic examination is thought to be unnecessary and undesirable except when additional information is essential. Urinary extravasation always indicates severe injury of the kidney and is felt to be a specific indication for operation. The presence or absence and the degree of hematuria are not criteria of the severity of renal damage.

Subcapsular Extravasation.—Baretz¹⁰ discusses renal hydrocele. It follows a form of renal trauma dependent on the following factors: (1) preexistent hydronephrosis or hydrocalix; (2) injury which produces extravasation from the pelvis or the calix beneath the renal capsule, and (3) slow healing of the tear. A mass in the abdomen in the region of one kidney, with or without a definite history of trauma; increasing size of the mass, increasing abdominal discomfort, and decreased urinary output are suggestive. Cystoscopic examination and retrograde pyelograms may reveal extravasation from the pelvis or calix to the surrounding sac. Early operative intervention with drainage may result in preservation of the kidney. If nephrectomy is indicated, a two stage procedure is advisable.

Aneurysm.—Lazarus and Marks¹¹ state that aneurysm of the renal artery is a rare clinical entity; they were able to collect only 75 cases from the literature and added a personal case. A history of trauma was elicited in 34.7 per cent of these cases. Among the other etiologic factors associated with this condition are systemic debilitating infections and atherosclerosis.

Pathologically, aneurysms may be classified as true or false. A true aneurysm is a saccular dilatation of an artery containing all the elements of the arterial wall; it results from weakening of the vessel wall, which is caused by involvement of the elastic fibers by sclerosis or fatty degeneration; this degeneration is due to some debilitating systemic infection or atherosclerosis. A false aneurysm is a saccular dilatation of an artery due to trauma, with resulting complete disruption of continuity of the arterial wall, either in part or in its entirety; the limiting walls of the aneurysm from without inward consist of adventitia, laminated blood clot and endothelium.

Small aneurysms of the renal artery usually produce no symptoms. Larger aneurysms, however, usually give rise to symptoms, the most common of which is pain in the loin (62.7 per

8. Bandler, C. G.; Pinck, B. D., and Roen, P. R.: Nephroptosis and Nephropexy: A Critical Review of Fifty-Five Cases, *New York State J. Med.* **44**:1541-1545 (July 15) 1944.

9. Adams, P.: Traumatic Rupture of the Kidney, *Ann. J. Surg.* **61**:316-323 (Sept.) 1943.

10. Baretz, L. H.: Renal Hydrocele: Subcapsular Renal Extravasation, *J. Urol.* **52**:184-198 (Sept.) 1944.

11. Lazarus, J. A., and Marks, M. S.: Aneurysm of the Renal Artery—True and False—with Special Reference to Preoperative Diagnosis, *J. Urol.* **52**:199-215 (Sept.) 1944.

cent of cases). A mass was felt in the loin in 30 per cent of the recorded cases.

The presence in the roentgenogram of an opaque ring shadow with a dense periphery in the region of the renal pelvis is an extremely valuable diagnostic sign of this disease.

The indicated treatment of an aneurysm of the renal artery is immediate nephrectomy, with ligation of the renal artery proximal to the point of origin of the aneurysm.

Lazarus and Marks report a case of aneurysm of the renal artery, associated with calculous pyonephrosis in which a correct preoperative diagnosis was made by observing a typical ring shadow on the roentgenogram in the region of the renal pelvis. Owing to the location of the aneurysm, the lesion was missed at operation but was clearly disclosed on pathologic examination of the extirpated kidney.

URETERS

Transplantation.—Young,¹² in discussing transplantation of the ureters into the rectosigmoid, states that Higgins' ability to find the ureters and to transplant them successfully into the bowel in babies only a few months old is a surgical triumph. He questions Higgins' assertion that unless the operation is done promptly in cases of exstrophy the ureters will rapidly dilate and become infected. He has seen many cases of exstrophy of the bladder in which the patients have grown to adolescence, even to 20 or 30 years of age, with no evidence of serious renal back pressure. Lower told Young that in only 2 of the 20 adults on whom he had operated for exstrophy were the ureters dilated when the transplantation was done. It therefore would seem not absolutely essential to operate on babies with exstrophy immediately but would seem safe to wait until later, when perhaps the exstrophy could be cured by operation and urinary control obtained by appropriate plastic procedures done at the same time on the new-formed vesical neck and penile urethra.

Many surgeons have been advising and carrying out removal of the bladder and transplantation of the ureters into the bowel in cases of epispadias. The operation for epispadias with incontinence is not a difficult plastic procedure, and Young believes that the wholesale use of ureteral transplantation and sacrifice of the bladder in these cases are absolutely unjustifiable. A number of boys with epispadias and incontinence on whom Young carried out his plastic procedure have now grown to adult age and have

not only normal micturition but normal powers; 1 has produced two children.

Nesbit,¹³ in discussing transplantation ureters into the rectosigmoid, affirms the merit made by Higgins that operation should be done early on children with exstrophy. He also states that he has had an opportunity to operate on 7 children under the age of 4 months; the youngest was 1 month old, the second procedure being done at the age of 7 months. Operation on these children was not difficult.

The author emphasizes one point: That only one layer of sutures over the anastomosis. Many times operators perform ureteral transplantation on the human being, and in anxiety to make a good anastomosis they put in a second line of sutures. This is only undesirable but distinctly disadvantageous.

Nesbit adds to the record the case of a child on whom he operated. She was 19 months of age at the time of transplantation of both ureters four years previous to this report. She became pregnant and delivered a stillborn child at 5 months, within a year after her operation. Subsequent marriage. Just a year ago she delivered a normal child by the birth canal.

Lower,¹⁴ in discussing transplantation ureters into the rectosigmoid, states the reason many dilated ureters are not found in the adult is that most of the children who have them acquire infection of the upper part of the urinary tract and die before they reach adult life. He does not transplant the ureters in cases of epispadias unless he fails to correct the condition by plastic operation.

Immediately after transplantation of the ureters, Lower often finds temporary dilation of the pelvis and calices; within a month or two these structures generally return to normal. He does not believe that excretory urography is a true test of renal function until he saw a case in which an excretory urogram showed a nonfunctioning kidney. Retrograde catheterization of the ureter a few days after this examination revealed a normal flow of urine from the kidney. The author therefore, does not accept the evidence of a nonfunctioning kidney from one excretory urogram as final.

The principal indication for ureteral transplantation is incontinence which cannot be corrected in any other way. Of course, the common cause is exstrophy, and it is desirable to correct it as early as possible.

13. Nesbit, R. M., in discussion on papers of Stevens and Lord, Higgins and Lower, *Tr. Am. A. Genit. Urin. Surgeons* 36:286, 1943.

14. Lower, W. E., in discussion on papers of Stevens and Lord, Higgins and Lower, *Tr. Am. A. Genit. Urin. Surgeons* 36:288-289, 1943.

12. Young, H. H., in discussion on papers of Stevens and Lord, Higgins and Lower, *Tr. Am. A. Genit. Urin. Surgeons* 36:286-288, 1943.

whether incontinence can be corrected simply by a plastic operation on the bladder.

Lower states that the patients have been followed over a period of years and have been restored to normal economic and social life. It is not known just how long the patients may live, but a number have survived twenty years or more in good physical condition.

Goldstein and Berman¹⁵ state that the conventional operation of ureterocutaneous transplantation for diversion of the urinary stream has had its disadvantages and ultimate discomforts. These are (1) periureteral infections with formation of an abscess and sloughing of the ureter, which defeat the purpose of the operation; (2) retraction of the ureteral stump; (3) obstructions in the ureter due to infection, causing strictures, or to the angulation of the ureters, and (4) inability to adjust properly an apparatus, principally because of insufficient length of the ureteral stump.

With the thought that there is a definite place for ureterocutaneous transplantation and that improvement is necessary in the performance of the procedure, both to obtain more comfort for the patient and to obviate unpleasant complications, Goldstein and Berman offer their modification of the conventional ureterocutaneous transplantation, which is performed in two stages, one to four days apart.

Cystoscopic examination should be performed and catheters left in the ureters if possible. An incision through the skin and subcutaneous tissue is made with the curve about 2 cm. more medial to the anterior superior spine than usual. The aponeurosis of the external oblique muscle is incised in the line of its fibers, and the internal oblique and transversalis muscles are split and cut. The fibers of the two muscles are then cut across for about 4 cm. in the line of the cutaneous incision. The underlying peritoneum is pushed medially by blunt digital dissection and is packed off. The ureter is identified and isolated for about 4 cm. above the bifurcation of the common iliac vessels and freed as far as possible toward the bladder; one should make certain to leave sufficient periureteral tissue, with the blood supply intact. A loop of ureter about midway in the incision is brought up on the anterior abdominal wall under tension, and a piece of tubing is placed beneath it. A black silk suture is placed through the periureteral tissue at its most distal point and brought out along the distal arm of the ureter onto the skin to serve as a guide in the second stage. The muscles are then approximated with surgical gut sutures proximal to, under and distal to the loop, space being left around

the two arms of the ureter. The fascia is sutured in a similar manner.

The second stage is simple. Three or four of the black silk sutures are removed from the distal portion of the wound, and the skin is spread apart by blunt dissection. Two of the interrupted chromic sutures in the aponeurosis of the external oblique muscle are removed distal to the loop, and these tissues are separated. With the black silk suture previously inserted into the distal arm of the ureter as a guide, this portion of the ureter is bluntly separated from the surrounding muscles and fascia down toward the bladder. The ureter is doubly ligated near the bladder, and a clamp is placed just proximal to this. The ureter is bisected, and the proximal stump is brought up on the anterior abdominal wall. A rubber tissue drain is placed down to the distal ureteral stump and brought out in the wound somewhat separated from the point of exit of the ureter. The distal portions of muscles, fascia and skin are closed around the ureter. A urethral catheter, which is later replaced by a Foley catheter, is inserted into the ureter, and petrolatum gauze is placed around the ureteral stump until healing takes place.

With this procedure, there is no retraction of the stump of the ureter, the blood supply remains adequate and there is no possibility of postoperative infection of the wound around the proximal portion of the ureter from infected urine. There results a ureteral stump which protrudes between 2 and 3 cm. from the anterior abdominal wall. The blood supply of the stump appears adequate.

The fundamental principle of the procedure is the establishment of the "right of domicile" of the ureter on the anterior abdominal wall. In the first stage a loop of the ureter is brought up; the ureter is not opened at this time but remains connected with the bladder and is allowed to function. The second stage of the operation involves ligation and bisection of the ureter near the bladder, the proximal stump being brought out to drain. Cystectomy may be carried out at the same time, if so desired.

Intubated Ureterotomy.—Davis¹⁶ discusses intubated ureterotomy and describes a new operation for ureteral stricture. He first applied the principle of the Ramstedt operation for pyloric stenosis to division of a stricture of the upper part of the ureter; the result was satisfactory. Since then a number of other surgeons have reported good results with this technic.

Davis reports a number of cases in detail. In general, the site to be dilated is cut longi-

15. Goldstein, A. E., and Berman, E. F.: Ureterocutaneous Transplantation: A New Procedure. *J. Urol.* 52:224-234 (Sept.) 1944.

16. Davis, D. M.: Intubated Ureterotomy: A New Operation for Ureteral and Uretero-Pelvic Stricture. *Tr. Am. A. Genito-Urin. Surgeons* 36:21-43, 1943.

tudinally, bands of ureteral tissue being left over the ureteral catheter or over a ureteral bulb. The open areas between the segments of ureteral tissue tend to grow together, filling in the fenestra made by the longitudinal cut. In other cases, large segments of the ureter are removed, with only a thin strand of ureteral tissue remaining; this tissue grows completely around the ureteral catheter, forming a new channel.

In this intubated ureterotomy, no effort is made to draw the tissue into a new form, and no sutures are used. The operation depends on the physiologic processes of repair of the tissues. The splint is a mold on which the tissues, by their own proliferation, reform the ureteral channel to normal size and shape. It must, therefore, be left in place until this proliferation is completed and the new channel lined with epithelium.

BLADDER

Diverticulum.—Hamilton¹⁷ reports a series of 22 cases of diverticulum of the urinary bladder encountered during the past sixteen years. In all the cases in this series the patients were men and the average age was 65 years. The diverticulum was removed in 9 cases: In 4 cases the prostate was removed at the same time; in 1 case the middle lobe only was removed at the same time; in 2 cases the prostatic portion of the urethra was digitally dilated, and in 2 cases the prostate was not touched.

It is only since the routine use of the cystoscope that the relative frequency of diverticulum of the bladder has been discovered. In 3 cases of Hamilton's series the cystoscope could not be passed through the prostate. The most common situation for a diverticulum is just above and lateral to a ureteric orifice, in an area where one often sees the earliest signs of fenestration in an otherwise normal bladder. The orifice of a diverticulum is usually circular, and the dark interior is not illuminated with the cystoscope lamp.

After the orifice of a diverticulum is discovered, a ureteric catheter is passed. If the whole catheter coils up in the diverticulum, a roentgenogram is made with the cystoscope still in position. Then a diverticulogram is taken after the injection of 20 cc. of a 12.5 per cent solution of sodium iodide along the ureteric catheter. This procedure is especially useful when the diverticulum is on the posterior wall of the bladder, as an anteroposterior cystogram will not show it and a lateral or an oblique cystogram is not always satisfactory. If the diverticulum is

large, the 20 cc. will not fill it completely; the case the cystogram will probably be better.

The two factors in the production of diverticulum appear to be weakness in wall, either congenital or acquired or a chronic obstruction to the outflow at the vesical neck or in the urethra.

Infection is liable to occur because of stagnation of urine within the diverticulum. Suprapubic drainage of the bladder may result from the first passing of the catheter. Infection once established in a bladder diverticulum is almost impossible to cure without removal of the diverticulum. Infection and infection predispose to formation of calculi. In Hamilton's series the cases of calculi in a diverticulum. (dumbbell calculus that had broken off.

A considerable number of cases of a diverticulum have been reported. Hamilton observed 1 case, an instance of malignant diverticulum, in his series. In another case a diverticulum was present in the bladder just over the diverticulum. In 2 cases perforation from ulceration following severe infection took place into the peritoneal cavity.

Hamilton discusses 6 cases in which the diverticulum was not removed. In 2 of these no treatment was carried out. In 3 cases of prostatic diverticulum was done, and in 1 case of endoscopic resection of the prostate was carried out. In 1 of the 3 cases in which prostatectomy was performed, a stone developed in the diverticulum two and a half years later, and there were no symptoms until a piece broke off. In another case death, due to pyelonephritis, occurred eleven months after operation. In the third case the patient lived for six years and died of senility. The patient with the endoscopic resection died ten years later of uremia. The urine remained infected throughout this time. In the last case in this series the diverticulum was not seen for three years after the diagnosis was made. He then had gross infection and uremia, no treatment having been carried out.

Burns¹⁸ states that diverticulum of the urinary bladder is most often seen in men between the ages of 50 and 70 with benign hyperplasia of the prostate. The development of a diverticulum should probably be ascribed to congenital and acquired factors. The symptoms are not pathognomonic and may even be absent. Complications include infection, calculus, hemorrhage, damage to the corresponding

17. Hamilton, A. J. C.: Diverticulum of the Urinary Bladder: A Series of Twenty-Two Cases (Honyman Gillespie Lecture), *Edinburgh M. J.* 50:513-534 (Sept.) 1943.

18. Burns, E.: Diverticula of the Urinary Bladder, *Selected Writings by Staff Members of Ochsner Hospital*, 3:40-48 (June 30) 1944.

and rupture. The diagnosis may be made from thorough cystoscopic examination of the bladder and complete roentgenologic studies of the entire urinary tract. The trend is toward conservatism in treatment. Retentive diverticula which are badly infected and diverticula associated with stones or neoplasms should be removed. Burns prefers to perform diverticulectomy first in cases in which treatment of obstruction at the vesical neck, as well as removal of the diverticulum, is required.

Trauma.—Ross¹⁹ states that injury of the bladder is not a common condition in civilian emergency surgical cases, but that the incidence increases as a result of the numerous penetrating wounds of modern warfare. He describes a series of cases which occurred within a brief period, each case being a classic example. A further point of interest is the absence of deaths. This observation is in disagreement with the view of earlier writers. In a series of 965 cases of abdominal injury sustained in World War I which were analyzed by Wallace, the bladder was injured in 45, or 4.66 per cent. Fullerton was able to collect a series of only 53 cases.

A full bladder is more prone to injury than one lying empty deep down in the pelvis. Larrey, who, as Napoleon's surgeon general, must have had a wide experience with wounds, pointed out this fact over a century ago. A full bladder presents a larger target than the empty organ; and if projecting above the pubis, it may be injured by a penetrating wound without damage to the bony pelvis.

The three main injuries are contusions, wounds and ruptures. Contusions are rare and difficult to recognize. They are usually due to prolonged and difficult labor, produce injury of the trigone muscle and may eventually predispose to the formation of a cystocele.

Wounds are generally of military origin and frequently of the penetrating type, although an occasional injury of the bladder during hysterectomy, especially vaginal hysterectomy, has been recorded. A punctured wound may temporarily seal itself off, as bullets tend to split the muscular fasciculi. In 4 of Fullerton's 53 cases the wound was situated in the suprapubic area; in 34 the wound of entry was in the region of the buttock, and in 5 the wound of exit was similarly situated. Thus, in 39 of 53 cases (75 per cent) a wound communicating with the bladder was found in the area of the buttock. In many instances the foreign body is retained, and in 10 of the 53 cases it was found in the bladder.

Inebriation is a well known predisposing factor in rupture of the bladder, especially when it is combined with a sharp blow on the hypogastrium. Not only is the bladder overdistended, but the abdominal musculature is not on guard.

Injuries of the bladder are divided into intraperitoneal and extraperitoneal lesions. Penetrating wounds of the abdomen usually cause intraperitoneal lesions, while missiles entering the pelvis via the buttock, thigh or perineum are more likely to produce extraperitoneal lesions. Intraperitoneal injuries usually affect the dome and the posterior wall of the bladder and lead eventually to peritonitis. Extraperitoneal lesions are situated anteriorly, laterally or at the base of the bladder and produce extravasation of urine and pelvic cellulitis.

In military practice extraperitoneal injuries are four times as common as intraperitoneal injuries, whereas in civil practice 80 per cent are intraperitoneal. Some authorities claim that in mining districts the percentage of extraperitoneal injuries rises with the frequency of fracture of the pelvis.

The majority of vesical injuries are complicated by injuries, sometimes even more serious ones, of other organs. Practically all extraperitoneal injuries are associated with fracture of the pelvis, the horizontal ramus of the pubis being most commonly involved. In general, intraperitoneal injuries are associated with peritonitis, and extraperitoneal injuries, with pelvic cellulitis.

For uncomplicated injuries the mortality has been estimated as greater than 50 per cent. The prognosis for intraperitoneal lesions is obviously graver when the small intestine is involved; "the picture is dismal in the extreme; in sixteen instances there was only one recovery." The importance of early operation is emphasized in cases of civil injuries. The mortality is 11 per cent if operation is carried out within twelve hours after the injury, 55 per cent if operation is delayed for twenty-four hours and 100 per cent if no operation is performed. It is evident, however, that the complications are also vital factors and that their presence or absence influences the final outcome to a great extent.

While in many cases intraperitoneal injury produces a high degree of shock, this is by no means an invariable accompaniment. The clinical features are conveniently divided into two stages: 1. During the first twenty hours severe shock and pain are accompanied with desire to void urine but with inability to do so. There are also symptoms of peritonism, slight generalized abdominal distention and some degree of rigidity. Free fluid is present. 2. After the first twenty hours

19. Ross, J. C.: Injuries of the Urinary Bladder, *Brit. J. Surg.* 32:44-49 (July) 1944.

signs of generalized peritonitis, and perhaps ileus, supervene.

With extraperitoneal injuries shock is not so prominent, but stranguria is usually a feature. It is important to distinguish the latter condition from rupture of the posterior portion of the urethra, with which the distended bladder can be readily felt. Later, pericystitis is followed by development of an abscess, which may point in the space of Retzius.

One must consider four cardinal features in making a diagnosis: history of injury in the region, presence of shock, inability to void urine and evidence of blood on passage of a catheter. Among the various diagnostic methods advised, intravenous pyelography appears innocuous; and, if time and facilities are available, it may prove helpful, if not diagnostic. On the other hand, the taking of a plain roentgenogram to determine the position of a foreign body or the presence of fracture of the pelvis is indicated if time, facilities and the patient's condition permit. Since in some cases the fecal fistula, if one is present, communicates with the rectum, sigmoidoscopy may be helpful under certain circumstances.

The passage of a catheter will demonstrate patency of the urethra; it may reveal distention of the bladder, and therefore absence of leakage (absence of more than a drop or two of urine suggests that the bladder has perforated, and an empty bladder indicates an intraperitoneal leak), and perhaps the presence of pure blood or blood-stained urine.

Cystoscopic examination, if done with care, involves no more danger than does catheterization, and sometimes the diagnosis cannot be made by any other method. Cystoscopic examination will give a correct diagnosis in 85 per cent of cases, and, provided subsequent operation is prompt, it does not add to the risk.

Amyloidosis.—Corbitt, Broders and Pool²⁰ report a case of amyloidosis of the urinary bladder. The patient, a woman aged 29, had had "bladder trouble" for ten years. Cystoscopic examination showed that the capacity of the bladder was reduced. A large fungiform growth extended from about 1 cm. above the left ureteral orifice up on the left lateral wall and involved the dome and part of the right lateral wall. Multiple specimens showed amyloid degeneration. Because of the location of the lesion and the possibility that it might overlie an infiltrating type of vesical neoplasm, it was thought advisable to

explore the bladder, with the intention of a segmental resection if possible. This was done and the lesion was found to be resectable. 50 per cent of the bladder was resected. Postoperative course was uneventful. Gross section removed was indistinguishable from plasm. Microscopic study revealed amyloid.

Actinomycosis.—Hatch and Wells²¹ report a case of actinomycosis of the urinary bladder which was apparently secondary to long-standing actinomycosis of the foot and lower part of leg. After several short periods of healing during the course of two years, the patient died of exsanguination.

Xanthic Calculus.—Butt and Holliman²² report a case of xanthic calculus, the nineteenth recorded in the literature. The stone was removed from the bladder of a white man aged 28. It was associated with constriction at the left terovesical junction and dilatation of the ureter and the left renal pelvis.

Gumma.—Ormond and Hemming²³ report a case of gumma of the bladder. The patient, a woman aged 60, had frequency, dysuria and hematuria. Cystoscopic examination revealed a large, ulcerated, protruding area on the left of the floor of the bladder, which simulated ulcerated incrustated cystitis or tumor of the bladder. The Kolmer and Kahn tests gave 4 plus reactions. On this basis, the condition was diagnosed as gumma of the bladder, and the patient was given antisyphilitic treatment. Cystoscopic examination a month later revealed that the bladder was clear although the mucosa of the bladder was somewhat edematous.

The symptoms of gumma of the bladder are not characteristic and are essentially those of vesical irritation. Hematuria may be one of the first symptoms and is usually present in cases of tertiary syphilis of the bladder. Frequency and dysuria are commonly associated with this condition. It has been stated that the more severe the closer the lesion is to the vesical orifice.

With tertiary syphilis of the bladder the gummatous ulcer is the most frequent lesion, although it may coexist with the papillomatous lesion. The ulcerating gumma may be either single

21. Hatch, W. E., and Wells, A. H.: Actinomycosis of the Urinary Bladder Complicating a Case of Madu Foot, *J. Urol.* 52:149-152 (Aug.) 1944.

22. Butt, A. J., and Holliman, H. D., Jr.: Xanthic Calculus: A Case Report, *J. Urol.* 52:89-91 (July) 1944.

23. Ormond, J. K., and Hemming, J. G., Jr.: Gumma of the Bladder: Report of a Case, *J. Urol.* 52:234 (July) 1944.

20. Corbitt, R. W.; Broders, A. C., and Pool, T. L.: Amyloidosis of the Urinary Bladder, *J. Urol.* 52:153-157 (Aug.) 1944.

ipple. It is usually grayish yellow, with infiltrated margins; the base is covered by a clot or necrotic tissue and is usually surrounded by a zone of inflammation. The most frequent site of a gumma is the region of the trigone, especially around the ureteral orifices, but the lesion may be present on any part of the bladder wall. Infection occurs as a result of the progress of gummatous ulcers and vesicoperitoneal and rectocolic fistulas.

Neither the picture obtained on cystoscopic examination nor the symptoms of this lesion are characteristic. Therefore the cystoscopic picture must be supported by the following factors: previous history of syphilis, evidence of active syphilitic lesion at the time, positive reactions to serologic tests, absence of other etiologic factors and progressive decrease in symptoms and disappearance of the lesions, as shown by repeated cystoscopic examinations following antisyphilitic therapy.

The treatment of gumma of the bladder is the specific treatment of syphilis. Local treatment is of no known value for this condition.

The prognosis on the whole is good. However, every effort should be made to safeguard against a relapse, and the patient should be followed closely for some time. Recurrences of syphilitic lesions of the bladder have been reported; however, these lesions have usually responded to renewed antisyphilitic therapy.

Stress Incontinence.—Macky²⁴ describes an operation for the cure of stress incontinence in females. Stress incontinence is a condition in which the urine passes uncontrolled from the urethra when the patient makes any effort tending to increase abdominal pressure.

Macky opens the bladder suprapubically. His main objective is to repair the internal sphincter, which is usually deficient posteriorly, without impairing the action of the muscle of the trigone. To do this it is necessary first to dissect the trigone free of the underlying sphincter and the circular inner muscle layer, rejoin the torn sphincter and then replace the trigone. This is done without disturbing the origin or insertion of the trigone muscle. The limits of the trigone are readily distinguished. There are two veins in the region of the ureteric orifices, which proceed along the lateral borders of the trigone. A small incision is made on the outer side of each of these veins and at the middle of the side of the trigone. The mucous membrane is divided

and the incision deepened by blunt dissection. A thread of surgical gut is drawn under the trigone, slightly above the middle. This can be held in a forceps, and it acts as a tractor. Incisions are then carried down on each side of the orifice, and the apical portion of the trigone is dissected until the lower portion inside the bladder is clear, the apex remaining in the posterior portion of the urethra. This provides a tunnel under this section of the trigone. Further dissection discloses the remains of the sphincter. A mattress suture is then passed through the tunnel, taking a good portion of the muscle on each side. When this is tied, the severed ends are drawn back to their original position beneath the trigone. A suprapubic drain is left in place for three weeks to prevent the repaired sphincter from being under strain.

PROSTATE GLAND

Operations on the Prostate.—Briggs²⁵ discusses the operations on the prostate reported on by candidates for membership in the American Urological Association.

The candidates average middle age before qualifying for membership in the association; most of them have had almost four years of hospital training, although not all that time has been devoted to urology.

Five hundred and seventy, or approximately 46 per cent, of 1,238 major operations reported were performed for some type of obstruction at the vesical neck.

Cystotomy was performed on 17 extremely ill patients because of intravesical hemorrhage, impassable strictures or some other compelling condition. Five hundred and fifty-three patients underwent some type of operation on the prostate, such as resection, one or two stage suprapubic prostatectomy or perineal prostatectomy.

The mortality for the entire series of operations, including the 17 "must" cystotomies, was 5 per cent. If the 7 deaths following the 17 cystotomies are excluded, as they should be because they were not performed on the prostate, the mortality for the 553 operations on the prostate was 3.9 per cent.

There were no deaths following the 33 perineal operations; for the 122 two stage suprapubic prostatectomies there was a mortality of 3.3 per cent; for the 338 resections, a mortality of 3.84 per cent, and, finally, for the 54 one stage supra-

24. Macky, F.: An Operation for the Cure of Stress Incontinence in the Female, *J. Urol.* 52:27-35 (July) 1944.

25. Briggs, W. T.: Analysis of Prostatic Operations Reported by Candidates for Membership in the American Urological Association, *J. Urol.* 52:153-160 (Aug.) 1944.

pubic enucleations, a mortality of 7 per cent, the highest rate observed.

The mortality of 3.84 per cent for the 338 resections is about what might be expected by any but the expert surgeon, since Nesbit reports a mortality of 3.6 per cent in 365 cases in which resection was performed by his residents.

The absence of death following the 33 perineal operations is in keeping with Young's statistics. For instance, in 1936 he reported that his last four resident urologists at the Brady Institute had performed 190 consecutive perineal prostatectomies, with 4 deaths, or a mortality of 2.1 per cent.

In his review of the postoperative notes on the resections, Briggs gained the impression that had it not been for the sulfonamide compounds the mortality for this group would have been much higher.

Emmett²⁶ discusses transurethral resection and open prostatectomy. In the ten years between 1933 and 1942, 8,954 transurethral resections were performed at the Mayo Clinic. During the same period transurethral resection was done in 102 cases in which suprapubic or perineal prostatectomy had been performed previously. The tissue removed in 66 of these cases was benign, while that removed in 36 cases was malignant. In 16 of the 36 cases in which the tissue was malignant, open prostatectomy had been done more than ten years before the transurethral resection. It must be assumed, therefore, that the original prostatectomy had been done for benign prostatic hyperplasia. This would tend to dispel the prevalent idea that so-called total prostatectomy necessarily gives protection from subsequent development of carcinoma of the prostate gland. It was also noted that in 7 of the 36 cases resection was performed within less than a year after prostatectomy. In 14 of the 36 cases the patients had suffered from obstructive symptoms continually since prostatectomy. The immediate results of transurethral resection in these cases were gratifying. Excellent results were secured in 29 cases.

In the 66 cases in which the tissue removed at transurethral resection was benign, the interval between prostatectomy and subsequent resection varied greatly. In 31 of these cases prostatectomy had been done more than ten years previously. In the majority of the cases prostatectomy had been performed by a surgeon well

trained in prostatic surgery; therefore, it can be assumed that the enucleation had satisfactorily approached completeness in most cases. In 20 cases open prostatectomy had been performed less than two years previously, in 8 cases the interval was longer but prostatectomy had been performed less than five years previously. In these 28 cases the results of prostatectomy can definitely be classified as satisfactory. The most common symptom in 66 cases was recurring obstruction of the ureter.

In 23 of the 66 cases the pathologic condition at the vesical neck was postoperative cicatrization or contraction. The scar tissue in 11 of these cases was dense and firm, and greatly suggested carcinoma. In the remaining 12 cases the obstruction was produced by various amounts of adenomatous tissue.

In 50 of the 66 cases the results were excellent, and in 13 cases the condition of the patient was greatly improved.

Emmett discusses incomplete and complete transurethral resection and reviews the experience at the Mayo Clinic for the period from 1933 to 1942 inclusive. In 1934, 696 transurethral resections were performed on 630 patients. In no instance was more than 55 Gm. of tissue removed at one stage, and in 87 per cent of the cases less than 35 Gm. was removed. Of the 696 resections, 64 (9.1 per cent) were second resections, which were done while the patient was still in the hospital because insufficient tissue had been removed to allow the patient to empty his bladder. These figures can be compared with those for 1942, during which 1,276 resections were performed on 1,233 patients. Of the number of resections, only 43 (3.4 per cent) were second resections or planned two stage procedures, done while the patient was still in the hospital. During 1942 more than 50 Gm. of tissue was removed (in one stage) in 21 cases and more than 100 Gm. in 13 cases. The largest amount of tissue removed at one stage during this year was 141 Gm. The mortality rate in 1934 was 0.3 per cent. In 1942 it was 1.1 per cent. It is evident that many of the resections in the earlier years were incomplete; consequently, it must be expected that some of the patients have required, or will require, another surgical operation on the prostate.

From six to ten years have passed since the early period of the incomplete type of resection, as carried out from 1933 to 1937 inclusive. Even for this period, in only 7.4 per cent of the cases in which the tissue removed at the first transurethral resection was benign did the pa-

26. Emmett, J. L.: Transurethral Resection and Open Prostatectomy: A Consideration Based on Ten Years of Experience with Transurethral Resection, *Surg., Gynec. & Obst.* 79:449-456 (Nov.) 1944.

ient return to the clinic for subsequent resection. If the years 1933 and 1934 are eliminated, the percentage of subsequent operations on patients whose original operation was done in 1935, 1936 or 1937 was only 4.4 per cent.

Emmett states that the main factor in recurring symptoms is incomplete removal of tissue. Many patients have enjoyed normal lives, free of urinary symptoms, for ten years or longer, and are still free of symptoms after an incomplete resection performed years ago. There seems to be no doubt that complete removal of the adenomatous tissue is desirable and guarantees the best immediate and late results. Nevertheless, it should also be appreciated that such a complete enucleation, performed transurethral, carries more operative risk than a less thorough operation.

Of the 8,465 transurethral operations performed at the Mayo Clinic from 1933 to 1942 inclusive, the mortality rate in cases in which more than 70 Gm. of tissue was removed was 2.6 per cent, as compared with a mortality rate of 1.2 per cent for the entire series.

Preparation before resection, when necessary, nearly always takes the form of drainage with a urethral catheter. Tests of renal function other than determination of the blood urea are rarely necessary. Long periods of preoperative preparation are unusual. The length of postoperative hospitalization also has been greatly reduced by transurethral resection. Among the 8,422 patients on whom resection was performed at the clinic from 1933 to 1942 inclusive, the average postoperative stay in the hospital was only eight and six-tenths days.

Marshall²⁷ states that perineal prostatectomy in general has been said to have certain advantages over transurethral and suprapubic methods, particularly in special instances in which the other approaches are contraindicated or would not obtain the desired result. The author points out the advantages of subtotal perineal prostatectomy over perineal enucleation, as follows: An unrecognized small carcinoma will probably be entirely removed, though for a recognized cancer Young's more radical operation is advised unless contraindicated. An infected, fibrotic or stone-bearing "capsule" can be removed. Better control of bleeding is obtained with a visual clamp and ligature. Marshall describes and illustrates a new method of subtotal perineal prostatectomy and discusses the results obtained in a consecu-

tive series of 18 cases. In his hands the method has been an improvement over perineal enucleation.

Carcinoma.—Herger and Sauer²⁸ state that 50 per cent of their patients receiving diethylstilbestrol medication exclusively responded with regression or softening of the prostate. This inclined the authors to believe that administration of estrogen without castration should have its place in selected cases of prostatic carcinoma. In their opinion, such treatment is indicated (1) for patients with operable carcinoma of the prostate who refuse radical operation; (2) for patients with moderately advanced lesions who have few, or no symptoms; (3) for patients with well differentiated adenocarcinoma, of comparatively low grade malignancy, in whom progression of the lesion is slow (this group includes patients who may live for many years without adequate treatment although the diagnosis of cancer has been proved by biopsy), and (4) for patients who refuse castration or patients for whom orchiectomy is contraindicated, for various reasons.

It is necessary to reexamine all these patients at frequent intervals, and castration should be carried out as soon as there are changes which point to progression of the lesions. Such changes are increase in size of the prostate, with progressive infiltration into the pelvis, development of obstructive symptoms, increase in the serum acid phosphatase activity and other signs and symptoms which suggest metastatic spread of the disease.

Herger and Sauer say that castration should be recommended for all patients with prostatic cancer in whom metastatic lesions are demonstrable and for patients with a type of lesion which usually has a tendency to rapid progression. In addition, castration should be carried out on patients who do not respond favorably to administration of diethylstilbestrol. This procedure has been employed by Herbst, who observed that castration was effective for patients who showed no improvement after treatment with estrogen.

The value of combined diethylstilbestrol medication and orchiectomy is undecided at present. In patients who respond favorably to castration, additional administration of estrogen may accelerate improvement, but Herger and Sauer's experience has shown that estrogen is ineffective for patients who fail to respond to orchiectomy.

27. Marshall, V. F.: Subtotal Perineal Prostatectomy: Presentation of a New Technique, *J. Urol.* **52**: 250-265 (Sept.) 1944.

28. Herger, C. C., and Sauer, H. R.: The Effect of Orchidectomy and Stilbestrol in Carcinoma of the Prostate, *Am. J. Surg.* **62**:185-200 (Nov.) 1943.

This view is supported by Herbst, who reported recently that even an increased dose of diethylstilbestrol had no influence on the downhill course of this disease.

Although Herger and Sauer have been impressed by the favorable results accomplished in numerous cases, they do not believe that castration or administration of diethylstilbestrol will result in cures. These methods of treatment are valuable adjuncts, which yield far more favorable results than does palliative roentgen irradiation or interstitial irradiation. Neither castration nor administration of diethylstilbestrol can substitute for surgical removal of carcinoma of the prostate when the gland is still encapsulated. Other methods of palliative treatment, such as transurethral resection or suprapubic cystostomy, will still retain their place in the treatment of carcinoma of the prostate in selected cases.

Barringer and Woodard²⁹ discuss the determination of acid and alkaline phosphatase in cases of carcinoma of the prostate in which the lesion has metastasized to bone and soft parts. The serum acid phosphatase level of two thirds of their patients with metastasizing carcinoma of the prostate was elevated when the patients were first examined.

The serum alkaline phosphatase level of all patients with osteoplastic involvement from carcinoma of the prostate was greatly elevated. In a few cases the metastatic involvement was osteolytic. In these cases the serum alkaline phosphatase value was normal or slightly elevated.

In patients whose serum acid phosphatase level was initially elevated and who showed a satisfactory clinical response to treatment with diethylstilbestrol or surgical castration, the value for the serum acid phosphatase fell promptly nearly to normal. Patients whose acid phosphatase level failed to show a conspicuous drop within two weeks after the institution of endocrine treatment likewise failed to show clinical improvement.

Two thirds of the patients whose serum alkaline phosphatase value was initially elevated showed a further increase after surgical castration, and one fourth, after the institution of diethylstilbestrol therapy. This rise was usually accompanied by an increase in the degree of osteoplastic involvement. It was not closely related to clinical response.

29. Barringer, B. S., and Woodard, H. Q.: Acid and Alkaline Phosphatase Determinations in Prostatic Carcinoma: Bone and Soft Part Metastases, *Tr. Am. A. Genito-Urin. Surgeons* 36:297-303, 1943.

URETHRA

Urethral Repair.—Corbus and Corbus³⁰ report a case of spontaneous closure of a urethrorectal fistula. The patient, a man aged 68, underwent a perineal prostatectomy. During blunt dissection of the rectum, a thinning of the rectal serosa was observed, although rectal examination showed no perforation. On the seventh postoperative day there were both fecal and urinary drainage through the perineal wound. Rectal examination revealed a mucosal perforation, 1 cm. in diameter, immediately proximal to the anal sphincter on the anterior wall. Suprapubic cystostomy was performed immediately, and the plain urethral catheter was replaced by a 30 cc. Foley catheter. Combined suction drainage, as suggested by Davis, was instituted with the aid of the Wangenstein decompression apparatus. Sulfaguanidine was given in full doses to aid in liquefaction, as well as sterilization of the intestinal tract. The perineal wound was irrigated twice daily, after which a gauze packing impregnated with balsam and a 2 per cent solution of silver to stimulate granulation was inserted. The patient was dismissed from the hospital five weeks later, with both the perineal and the suprapubic fistula closed and no evidence of urethrorectal communication.

Uhle and Erb³¹ discuss the incidence, mechanism of trauma and surgical aspects of intrapelvic rupture of the urethra as a complicating factor of fracture of the pelvis. With the more severe types of trauma, in which complete severance of the urethra occurs, with or without displacement of the prostate, immediate suprapubic drainage should be instituted. At the same time an attempt should be made to reunite the severed portions of the urethra by retrograde catheterization. If this is impossible, because of hemorrhage, shock, intra-abdominal injury or extensive trauma to the urethra and bladder, secondary perineal section and urethral anastomosis must be performed in the shortest time compatible with the patient's safety. In 2 of the cases reported by the authors, dense strictures had replaced the membranous portion of the urethra. The patients when admitted to the hospital had draining suprapubic sinuses of four and nine months' duration. Secondary perineal operation for restoration of urethral continuity had not been performed. The technic of perineal section, excision of the stricture and anastomosis

30. Corbus, B. C., Jr., and Corbus, B. C., Sr.: Management of Urethro-Rectal Fistula: Review of Literature and Report of a Spontaneous Closure, *J. Urol.* 52:61-62 (July) 1944.

31. Uhle, C. A. W., and Erb, H. R.: Reconstruction of the Membranous Urethra: Case Reports, *J. Urol.* 52:42-60 (July) 1944.

of the anterior and posterior portions of the urethra, with preservation of the external sphincter mechanism, is described.

McCague and Semans³² discuss the management of traumatic rupture of the urethra and ladder complicating fracture of the pelvis. In 33 (or 17 per cent) of a series of 780 cases of fracture of the bony pelvis, rupture of the urethra or bladder was a complication. These consisted of 99 cases of intrapelvic rupture of the urethra, 1 case of rupture of the anterior portion of the urethra, 22 cases of rupture of the bladder and 11 cases of combined rupture of the urethra and bladder.

A critical analysis of this large series of cases was made. This study has established certain principles of treatment as essential in avoiding both the immediate mortality and the late complications. The mortality has been reduced from 48 per cent (reported by Besley through 1907) to 23 per cent (McCague and Semans, 1942).

The reduction in mortality depends on the following principles: (1) early and accurate diagnosis; (2) adequate treatment of surgical shock; (3) provision of urinary drainage; (4) surgical drainage of the traumatized tissue, and (5) immobilization of the bony pelvis.

The diagnosis is not difficult. The patient is usually in profound shock. The fractured pelvis causes pain on movement. The legs are rotated outward and cannot be moved. Compression of the pelvis causes exquisite pain and frequently crepitus. The ruptured urethra produces frank blood at the external urinary meatus. On rectal examination, the normal contour of the prostate may be masked by a hematoma. If the urethra has been severed, the prostate is displaced and is not palpable. Unless there is an associated rupture of the bladder, extravasation of urine does not occur early. If there is also rupture of the bladder, the clinical picture differs. There is usually pronounced tenderness in the lower part of the abdomen over the site of the rupture. Instrumentation, including catheterization, contributes little and produces trauma in a patient already in shock.

The most common cause of early death is progressive shock. This is secondary to the crushing blow to the pelvic bones and soft parts. Bleeding from other ruptured viscera may be contributory. Immediate intravenous administration of blood and plasma is strongly indicated.

Extravasation occurs late in cases of urethral rupture unless the bladder is also perforated. Therefore, once the diagnosis is established and

the shock relieved, the urine must be diverted by cystostomy. In cases of partial rupture drainage with a urethral catheter alone has been used. But without cystostomy an occluded urethral catheter will soon cause urinary extravasation from the site of rupture. The combined use of a suprapubic and a urethral catheter is ideal. The latter establishes the continuity of the urethra. Sutures are not necessary. The urethra heals rapidly around the catheter.

The soft tissues about the urethra and bladder are usually damaged and contain extravasated blood, and sometimes urine. Sepsis spreads quickly unless hemorrhage into these tissue spaces is completely controlled and the spaces themselves widely drained. A rapid perineal incision, to establish dependent periurethral drainage, is desirable if the patient's condition permits. If not, this procedure can be carried out later. If there is intraperitoneal rupture of the bladder, the peritoneal cavity, as well as the bladder, must be drained to avoid generalized peritonitis.

The fractured pelvis is best treated by immobilizing the pelvic girdle with a firm binder and suspending the pelvis in a sling. The legs are put in extension. This has the added advantage of bringing the two ends of the ruptured membranous portion of the urethra in better apposition.

For reduction of morbidity, unnecessary investigative procedures must be eliminated. The diagnosis is established by physical examination alone, without recourse to catheters and instruments. Preservation of the continuity of the urethra must be effected early, to prevent fibrous tissue from filling the large gap between the torn ends of the urethra. With the legs in extension, anastomosis of the torn ends is unnecessary. Areas of extravasation around the bladder and urethra are thus adequately drained through the abdomen and through the perineum. Except for injuries confined to the anterior portion of the urethra, cystostomy is preferable to drainage with a urethral catheter alone. Secondary infection, sepsis and death have occurred in cases in which only perineal section and anastomosis of the torn ends of the urethra were employed. The same is true with simple urethral catheterization. Almost invariably there is leakage into the mutilated and devitalized tissues at the site of rupture, with subsequent sepsis.

If the urethral continuity is preserved, early stricture of the region of rupture is unlikely. However, in cases of injuries of the bulbous portion of the urethra, produced by a person's falling astride a hard object, healing may result in a constricting scar. Impotence may result if there has been severe damage to the nerve and blood

32. McCague, E. J., and Semans, J. H.: The Management of Traumatic Rupture of the Urethra and Bladder Complicating Fracture of the Pelvis, *J. Urol.* 52:36-41 (July) 1944.

supply of the corpora. Nothing has proved successful in preventing this distressing complication.

Fifty-one consecutive cases of fractured pelvis observed in three years (1940 to 1942 inclusive) were studied recently. The average age of the patients was 40 years. There were 6 cases of intrapelvic rupture of the urethra. All were observed within a few hours of the time of injury. On physical examination there was evidence of shock. Discoloration of the scrotum, caused by hematoma, was observed in 2 cases. The operative procedure was similar in all of the 6 cases. As soon as the diagnosis was made and surgical shock was relieved, suprapubic cystostomy was done. In all cases it was feasible at the same time to preserve the continuity of the urethra with a splinting catheter. Perineal drainage was then established by rapid section. In all but 1 case the patient had complete urinary control on discharge from the hospital. Of the 51 cases there were 6 cases of extraperitoneal rupture of the bladder. Suprapubic cystostomy was carried out a few hours after the accident in all but 3 cases. In 2 of these cases death occurred from shock before operation could be done, in spite of intensive therapy. In another case urethral catheterization only was used, extravasation not being evident for eighteen hours following the patient's admission to the hospital. In all cases except the 2 in which death occurred from shock the patient was discharged as well. In these 6 cases there was no intraperitoneal rupture. Extraperitoneal drainage was employed in all cases. The average stay in the hospital was five and one-half weeks.

Urethritis.—Grenley³³ states that in many cases of urethritis the stigmas attached to the term "venereal disease" are lacking and yet the cause, symptoms, course and treatment follow closely those of urethritis following gonococcal infection. He discusses 180 cases of nongonococcal urethritis. There was a history of recent sexual intercourse, with a latent period of less than sixteen days. In no case was there any evidence, either in the history or during the course of the illness, of preexisting infection of the genitourinary tract. The possible causes included direct contact with a woman infected with other organisms than the gonococcus and the use of various irritating chemicals by the woman or by the soldier as prophylaxis. Twenty-eight and nine-tenths per cent of the patients used the official Army prophylaxis; 17.8 per cent used mechanical means (rubber condom), and

46.1 per cent used no prophylaxis. No organisms were found in the urethral discharge in 42.8 per cent of these patients. There were genitourinary complications in 13.3 per cent of the patients, of which urethral stricture was by far the most common. Twenty-nine and four-tenths per cent of the patients required no active treatment; 52.3 per cent were apparently cured with chemotherapy. In uncomplicated cases the average time actually lost from duty was twenty-one and one-half days.

Oard and associates³⁴ report on the use of penicillin sodium in the treatment of 411 patients with urethritis following gonococcal infection. Combined treatment with moderate doses of sulfathiazole and small doses of penicillin sodium was used with 232 patients. Gonococcal urethritis in the Negro is more susceptible to treatment with penicillin and with penicillin and sulfathiazole combined than it is in the white race. Sulfathiazole and penicillin appear to enhance the effect of each other against *Neisseria gonorrhoeae*. The combined use of moderate amounts of sulfathiazole and of penicillin is a safe, rapid, efficient and economical method of treating gonococcal urethritis.

TESTES

Tumors.—Barringer,³⁵ in discussing tumor of the testis, describes the results of autopsy in some 35 cases of teratoma of the testis. The observations are amazing and instructive. Among other results, in practically 100 per cent of the cases in which the patient died, there was bilateral abdominal invasion, due to involvement of the spleen, the kidney, the retroperineal lymph nodes or the lymph nodes which had crossed over. In a large percentage of cases there was renal or perirenal invasion by the tumor. In 75 per cent of all cases in which the lungs were involved, the liver also was affected.

Smith,³⁶ in discussing tumor of the testis, states that he personally has not performed Hinnman's operation because the metastatic lesions of the radiosensitive testicular tumor can be controlled by roentgen ray therapy and in a considerable proportion of the cases the lungs are involved early in the course of the disease. He feels unable

34. Oard, H. C.; Jordan, E. V.; Nimaroff, M., and Phelan, W. J.: The Treatment of Gonorrheal Urethritis, with Sulfonamides and Penicillin Combined, *J. A. M. A.* 125:323-325 (June 3) 1944.

35. Barringer, R. S., in discussion on papers of Smith and Barringer and Woodard, *Tr. Am. A. Genito-Ur. Surgeons* 36:305, 1943.

36. Smith, G. G., in discussion on papers of Smith and Barringer and Woodard, *Tr. Am. A. Genito-Ur. Surgeons* 36:307-308, 1943.

33. Grenley, P.: Non-Specific Urethritis of Venereal Origin, *J. Urol.* 52:92-97 (July) 1944.

differentiate lesions which would not be radio-sensitive.

Smith says that this radical operation may be of value for patients who have certain types of teratoma; on the other hand, metastases from teratoma, which in itself is largely resistant to radiation, may be radiosensitive. Hinman himself said that operation is useless when the metastatic lesions are palpable; this eliminates a large portion of the cases. It seems, therefore, that the testicular tumors suitable for this operation are so few as to be difficult to identify.

Smith has not used preoperative roentgen ray therapy because, in the first place, he cannot see why the procedure of cutting down on the spermatic cord and immediately ligating it, before the testis is touched, will induce spread of the metastatic lesion. The distinct disadvantage of reoperative irradiation is that it may make impossible the pathologic diagnosis of the tumor which is removed.

In addition, some testicular tumors are not what one thinks they are, and to give a patient an adequate course of irradiation only to find out he has a fibroma or a leiomyofibroma is absurd.

EPIDIDYMIS

Malignant Tumors.—Crabtree³⁷ reports a case of teratoma of the epididymis. He states that at present there are not sufficient data to determine whether or not adult cells of the epididymis can give rise to malignant tumors. It appears that this is possible, at least for certain kinds of tumors. Tumors which simulate those characteristic of the testis may, and probably do, arise from fetal implants of cells from the testis. The clinical behavior of primary malignant tumors of the epididymis, especially carcinoma and sarcoma, is not characteristic of that of cytologically similar tumors when they occur in the testis. When both the testis and the epididymis are involved, clinical progress is more nearly like that of tumors of testicular origin. It is probable that any type of malignant tumor which is common to the testis may occur in the epididymis, but the frequency of occurrence is greatly reduced below that in the testis.

SPERMATIC CORD

Tumors.—Shivers³⁸ reports a case of primary rhabdomyosarcoma of the spermatic cord with

secondary invasion of the epididymis and testicle. Only a few extratesticular myogenic tumors have been reported as invading the testicle, and their origin in most instances has been questioned. Myogenic tumors involving the testis should usually be considered as a one-sided development of a teratoid neoplasm; but in the case reported, from the observations at operation and the reports of pathologists. Shivers feels that he is justified in making a diagnosis of primary rhabdomyosarcoma of the spermatic cord with metastatic involvement.

PENIS

Trauma.—Roth and Warren³⁹ report 2 cases of traumatic avulsion of the skin of the penis and scrotum. They state that total, or nearly total, denudation of the penis is satisfactorily handled by the use of split thickness grafts, and this technic is facilitated by the use of the Padgett dermatome. In many cases of so-called complete avulsion of the scrotum, the avulsion is not actually complete in that small remnants of viable scrotal skin are attached somewhere to the margins of the wound. To ignore these small bits of scrotal skin is to ignore the almost incredible regenerative power of the scrotum, which makes possible a primary plastic repair. Primary plastic repair of the scrotum as described is technically easy, gives far superior anatomic results and eliminates the necessity for later time-consuming plastic reconstructions.

CHEMOTHERAPY

Penicillin.—Thompson⁴⁰ states that penicillin is a particularly valuable drug for the treatment of gonorrhea. The most practical method of administration is intramuscular injection of a solution containing 5,000 or 10,000 units per cubic centimeter. Doses of 20,000 units injected every three hours until 100,000 units has been given will result in cure in fully 98 per cent of cases.

Penicillin is unstable in solution, and at room temperature it rapidly loses its antibacterial power. Solutions should be freshly prepared and kept in the icebox between injections.

Penicillin is an extremely useful drug in the treatment of various nonspecific infections of the genitourinary tract. If the infection is caused by penicillin-sensitive organisms, the result of

37. Crabtree, E. G.: Malignancy of the Epididymis, with Report of a Case of Teratoma of the Epididymis. *Tr. Am. A. Genito-Urin. Surgeons* **36**:119-127, 1943.

38. Shivers, C. H. deT.: Rhabdomyosarcoma of the Spermatic Cord. *J. Urol.* **52**:266-274 (Sept.) 1944.

39. Roth, R. B., and Warren, K. W.: Traumatic Avulsion of the Skin of the Penis and Scrotum. *J. Urol.* **52**:162-168 (Aug.) 1944.

40. Thompson, G. J.: The Clinical Use of Penicillin in Genitourinary Infections. *J. A. M. A.* **126**:433-437 (Oct. 14) 1944.

treatment is excellent. In most cases, however, the infection is mixed and the result of therapy is not dramatic. Nevertheless, it is worth while. Administration of penicillin combined with other urinary antiseptics in these cases might well be superior to other methods of treatment.

The results of treatment in urologic cases can be determined well by repeated staining of the urethral or prostatic secretions or the sediment of the centrifuged urine with Gram's stain.

Treatment with penicillin is so devoid of toxic reaction that there is no reason to outline difficult schedules or to use complicated methods. The physician need not be fearful of using too much of the drug and should follow the dictum that the dose of any medicine is "enough."

Greenblatt and Street⁴¹ state that penicillin is an effective drug for the treatment of chemoresistant gonorrhea in women. One hundred and nine patients received courses of penicillin therapy. Five hundred and fifty-one women were studied for venereal diseases, and for 61 per cent laboratory evidence to support the diagnosis of gonorrhea was obtained. During the period of observation in this series, treatment of 5 women with penicillin resulted in failure. A favorable response was obtained after a second course of therapy.

The dose of penicillin should not be reduced to the minimum necessary for good results. It should be maintained at a sufficiently high level so that the development of penicillin-resistant strains is thwarted. To this end it is recommended that 150,000 units be used, although good results may be obtained with as little as 60,000 units. The authors sound the warning note that there may be asymptomatic carriers and that penicillin-resistant strains of gonococci may appear.

Sternberg and Turner⁴² state that studies have been carried out in fifteen selected Army hospitals with a view to determining as rapidly as possible time-dosage factors in the treatment with penicillin of gonorrhea which is resistant to sulfonamide drugs. A total of 1,686 patients refractory to at least two courses of a sulfonamide compound, and in some cases to artificially induced fever, were treated with total doses varying from 40,000 to 160,000 Oxford units per patient, the individual dose being 10,000 or

20,000 units administered intramuscularly every three hours.

These studies showed penicillin to be remarkably effective in the treatment of gonorrhea, usually causing symptoms to disappear and results of bacteriologic cultures to become negative within forty-eight hours. One course of treatments effected cures in 98 per cent with a dose of 160,000 units per patient, in 96 per cent with a dose of 80,000 to 120,000 units and in 95 per cent with a dose of 50,000 units. No significant difference in the final results was noted when a given dose was administered in individual injections of 10,000 and in 20,000 units. Furthermore, little advantage was gained by prolonging the period of treatment schedules beyond twelve hours. Factors such as duration of infection, previous fever therapy and race appear to have no effect on the results of therapy.

Of the 126 patients who failed to respond to one course of treatments with penicillin, 85 were given a second course, with a dose of 100,000 units. Of these patients, 78, or 91.8 per cent were cured. Thus, with a second course of treatments 99 per cent of cures was obtained. No patient in the entire series proved to be resistant to penicillin.

Complications of gonorrhea responded well to penicillin, although the more serious complications required prolonged treatment with a large dose. Reactions to penicillin were inconsequential, and in no instance was it necessary to discontinue treatment because of such a reaction.

Because of the known effects of penicillin on *Treponema pallidum*, the possibility of masking or delaying the development of early syphilis must be considered.

Finally, it should be recognized that the treatment of gonorrhea has been completely revolutionized in the past few years, first, by the introduction of sulfonamide drugs and, more recently, by the development of penicillin. It is clear that the management of gonorrhea now belongs within the sphere of the chemotherapist and that local treatment is rarely necessary, and may do more harm than good.

Sulfonamide Compounds.—McClelland⁴³ states that one of the hazards of the use of sulfonamide drugs is the development of anuria in a person who takes small doses. This condition may be serious, and an effort is being made to avoid it, if possible, or to correct it.

The problem which faces the urologist as soon as he sees a patient with anuria from any cause is to decide whether the anuria is a result of

41. Greenblatt, R. B., and Street, A. R.: Penicillin for the Treatment of Chemoresistant Gonorrhea in the Female, *J. A. M. A.* 126:161-163 (Sept. 16) 1944.

42. Sternberg, T. H., and Turner, T. B.: The Treatment of Sulfonamide Resistant Gonorrhea with Penicillin Sodium: Results in 1,686 Cases, *J. A. M. A.* 126:157-160 (Sept. 16) 1944.

43. McClelland, J. C.: Sulfonamide Anuria, *Trans. A. Genito-Urin. Surgeons* 36:133-137, 1943.

onfunction of the renal parenchyma or of an obstruction, usually due to crystals, somewhere in the urinary passages. This will lead to distention of the renal pelvis and resultant pain and tenderness on the side of obstruction. If there is much distention, enlarged kidney may be felt. In cases of this type of anuria a ureteral catheter may be introduced to the area above the obstruction, with the result that the kidney increases its output of urine and the patient recovers. It is no great problem to decide whether there is distention of the pelvis. This can be ascertained by the presence of tenderness over the distended kidney. The ureteral catheter will relieve the distention. If by any chance the catheter cannot be passed to the distended renal pelvis, operation must be resorted to to relieve the distention. If one cannot be sure, one is justified in passing a ureteral catheter.

The intravenous use of sodium bicarbonate places an alkaline medium in the tubules of the kidney as an aid in dissolving any crystals of the sulfonamide drug which might be blocking the tubules in the kidney. It is known that the solubility of sulfadiazine and sulfathiazole increases rapidly as the p_H increases from 7 to 8.

In the department of pathology at the Banting Institute, in Toronto, slides of tissue were examined from similar cases in which death occurred after therapy with sulfonamide drugs. In 1 case the lungs, kidneys and spleen showed areas which were granulomatous and contained giant cells. One group of observers thought that these lesions were the granulomas of glanders, while another group stated that the granulomas were evidence of toxicity. In another case, in which a soldier who had treated himself for gonorrhea died of anuria, there were a small quantity of fibrinoid material in Bowman's capsule and eosinophilia in the interstitial tissue but no evidence of thrombosis. Thus, in these 2 cases the microscopic pictures of the renal parenchyma were different. The cause is thought to be a toxin, but what, one cannot say; nor do the fatal cases show a uniform picture.

McClelland reports a case in which the patient was given 30 grains (2 Gm.) of sulfathiazole and 150 grains (9.6 Gm.) of sulfapyridine in forty-eight hours. Anuria developed, and the patient died early, on the seventh day. The pathologic changes were not extensive, nor did they seem sufficient to cause anuria and death. The ureters and the tubules were not blocked with crystals.

Zide⁴⁴ reviews the histories in 10 cases, in which there were eleven renal reactions to sulfon-

amide drugs, one to sulfathiazole and ten to sulfadiazine. The minimal intravenously administered dose before renal symptoms occurred was 7 Gm. of sodium sulfadiazine. The minimal time before onset of renal symptoms was twenty-four hours. Two delayed reactions occurred, one six days and the other twelve days after administration of sulfadiazine was discontinued. During renal complications the urinary reaction to litmus paper was acid in 8 instances, alkaline in 1 and undetermined in 2. The sulfadiazine level of the blood ranged from 23 to 4 mg. per hundred cubic centimeters at or about the time of the renal reactions, the majority being over 8 mg. per hundred cubic centimeters. The treatment of all the patients in this series was conservative, with an unsuccessful attempt at manipulative treatment of 1 patient, who responded later to conservative therapy. The end results were cure of the original condition and the renal complications in all cases.

Ormond and Roth⁴⁵ state that recent reports indicate that the already wholesale use of sulfonamide drugs appears destined to increase. This is due not only to a wider application in the therapy of recognized diseases and to the development of new and more effective derivatives but to the use of these drugs in prophylaxis against infection. The authors review a few recent cases illustrating the nature of the dangers involved.

They say that there is irrefutable evidence that patients can be sensitized to sulfonamide derivatives and that the majority of the undesirable reactions occur in persons who have been sensitized by previous courses of the drug. This sensitization can be accomplished even by topical application of sulfonamide compounds.

From the point of view of pathologic lesions, three types of renal damage from sulfonamide drugs are recognized: first, frank obstruction, due to the deposition of crystals of the acetylated drug; second, widespread focal necrosis in which the kidney is only one of many organs involved in which renal obstruction provides the frequently fatal result; third, acute toxic nephritis in which focal necrosis and crystals are absent but in which anuria and uremia are the striking clinical features.

In respect to therapy, Ormond and Roth urge the early institution of intravenous administration of fluid, with appropriate use of a sixth molar solution of sodium lactate when acidosis is a factor and with administration of saline solution in accordance with the blood chloride

44. Zide, H. A.: Renal Complications of Sulfonamide Administration: Report of Reactions from Sulfathiazole and Sulfadiazine, *J. Urol.* 52:275-282 (Sept.) 1944.

45. Ormond, J. K., and Roth, R. E.: Recent Cases Illustrating Dangers of the Sulfonamide Drugs, *Tr. Am. A. Genito-Urin. Surgeons* 36:139-145, 1943.

values. The balance of the required fluids should be a 5 per cent solution of dextrose. Cystoscopic examination with ureteral catheterization and pelvic lavage with a warm solution of sodium bicarbonate should be undertaken when crystalluria is present and seems to be a possible cause of obstruction. Alkalinization of the urine with large doses of sodium bicarbonate given by mouth is likewise a rational procedure when crystalluria is present and seems to have been of distinct benefit in cases in which crystals played no part. Short wave diathermy of the kidneys has appeared to be a useful adjuvant in several cases. On theoretic grounds, diuretics which might possibly have a toxic action on the kidneys are contraindicated.

HERMAPHRODITISM

McIver, Seabaugh and Mangels⁴⁶ state that in the majority of the reported cases of true hermaphroditism the condition has been classified as bilateral and in the greater proportion of these cases the genitalia have presented. In these respects the condition in first of 2 cases reported was typical. It was atypical in that a tube and an ovary without a uterus were present. Also at variance with the usual findings were the union of the tube and the vas deferens and their termination in a blind fibrous cord, the vas deferens having no connection with the deep portion of the urethra. In 8 of the 13 cases reviewed the anomaly was bilateral. It was impossible in these cases to distinguish clearly between the testicular and the ovarian tissue of the two gonads.

A second case reported was not a typical instance of hermaphroditism. Except for the absence of the testis on the right side, the external genitalia were in a normal condition, which occurs rarely in cases of this type. The tube, present on the right side, was involved in an infectious process, which produced acute episodes in the right lower quadrant of the abdomen and presented a pyosalpinx at the time of removal. These features appear to be unique, for a review of the literature did not reveal any similar instance. This case, in McIver, Seabaugh and Mangels' opinion, should be classified among instances of true lateral hermaphroditism. It is unfortunate that no pathologic evidence was available to confirm this contention. The finding of live motile sperm in the ejaculated fluid established the presence of active testicular tissue, but it did not preclude the presence of ovarian tissue also.

46. McIver, R. B.; Seabaugh, D. R., and Mangels, M., Jr.: True Hermaphroditism: A Report of Two Cases. *J. Urol.* 52:67-85 (July) 1944.

INFECTIONS OF THE URINARY TRACT

Cook⁴⁷ calls attention to an interesting, but small, group of patients with infection of the urinary tract. Repeated stains and cultures of the urinary sediment from patients with this type of infection repeatedly yield negative results. The symptoms of this type of infection are the same as those of the more common bacterial infections of the urinary tract, but usually more severe. Examination of the urinary sediment and cystoscopic study reveal definite evidence of infection. Rarely is there an associated renal condition, but it has been found in some instances. Because of the existence of pyuria without demonstrable organisms in the smear, this clinical entity has frequently been confused with tuberculous infection. It goes without saying that a diagnosis of tuberculosis of the urinary tract should never be made on the basis of the presence of sterile pyuria alone, without corroborative evidence of an infection with acid-fast organisms.

The treatment of infection without demonstrable organisms is almost specific. The usual chemotherapeutic agents, such as mandelic acid and the sulfonamide drugs, are of little value. Arsenical preparations, given intravenously, are most useful, and usually two or three doses of neoarsphenamine (0.2 to 0.37 Gm.), given five days apart, will sterilize the urine. In a number of instances removal of foci has contributed greatly to the clearing up of such infections. The relationship seems definite, as frequently the removal of foci brings about a temporary increase in symptoms.

Helmholz⁴⁸ in an editorial on treatment of infections of the urinary tract in childhood, states that recognition of bacteria as the cause of these infections penetrated rather slowly into the practice of pediatrics and urology. The first micro-organism causing an infection of the urinary tract in childhood was isolated by Escherich; it was a colon bacillus, which under the accepted bacteriologic nomenclature is known by the name of *Escherichia coli*. Later it became evident that a number of bacteria can produce infections of the urinary tract, that these bacteria differ in their susceptibility to various antiseptics and that different strains of the same micro-organism may do so.

Earlier, acidification and alkalinization of the urine were advocated for the treatment of pyelitis. With the aid of determination of the

47. Cook, E. N.: Infections of the Urinary Tract Without Demonstrable Organisms. *Proc. Staff Meet. Mayo Clin.* 19:377-380 (July 26) 1944.
48. Helmholz, H. F.: Treatment of Urinary Infections of Childhood, editorial. *Surg., Gynec. & Obst.* 79:557-558 (Nov.) 1944.

hydrogen ion concentration, it was shown that a p_H of 4.6, on the acid side, or of 9.0, on the alkaline side, was necessary to sterilize urine infected with a given colon bacillus. With the introduction of methenamine as a urinary antiseptic the importance of the hydrogen ion concentration of the urine became emphasized. Methenamine itself is without bactericidal power, but when the hydrogen ion concentration falls to 5.5 or less, formaldehyde is liberated and displays bactericidal potency.

Often no attention was paid to the necessity of acidifying the urine sufficiently, and then the medication was not successful. With acidification, the dose required produced irritation of the bladder in some cases, with hematuria.

Helmholz and Clark introduced the ketogenic diet for the treatment of infections of the urinary tract. Betaoxybutyric acid is excreted by the human kidney in high enough concentrations to sterilize the urine when it has the proper p_H . The lower the p_H , the lower is the concentration of the acid necessary to kill bacteria. The introduction of mandelic acid made it possible to give an organic acid by mouth, rather than to produce it by means of a high fat diet. Mandelic acid, too, is bactericidal only at a p_H of 5.5 or less in concentrations in the urine which can be achieved without danger of renal irritation.

The most recent addition to the urinary antiseptics is the group of sulfonamide compounds. Their rapid excretion, even by the damaged kidney, their action in acid and alkaline urine and their bactericidal action when given in small amounts which are not likely to produce renal damage make them the urinary antiseptics of choice. However, the great drawback of the entire group is their lack of action on infections with *Streptococcus faecalis*.

This fact has introduced for the first time the necessity of determining the nature of the infection. Hitherto, certain bacteria might be slightly more resistant than others but could be inactivated by slightly longer treatment or by increase in the dose. *Str. faecalis* grows luxuriantly in urine containing one of the sulfonamide compounds in concentrations which will kill the usual gram-negative bacilli. Since the introduction of the sulfonamide compounds it has been realized how frequently mixed infections with gram-negative bacilli and *Str. faecalis* exist; initial cultures may show apparently pure cultures of gram-negative bacilli, but after several days' treatment with one of these drugs pure cultures of *Str. faecalis* may be found.

Of the sulfonamide compounds, sulithiazole or sulfadiazine is the drug of choice for all infections but that due to *Str. faecalis*. For infections with *Str. faecalis* mandelic acid is the drug

of choice. This leaves without adequate treatment only infections with *Str. faecalis* in patients who have damaged kidneys, since neither the required p_H nor the required concentration of the drug may be obtainable.

MALE CLIMACTERIC

Heller and Myers⁴⁹ discuss the symptoms, diagnosis and treatment of the male climacteric. The diagnosis of the male climacteric was established in 23 cases by the finding of pronounced elevation in excretion of gonadotropin, comparable quantitatively to that occurring in castrated men. This was corroborated in all 8 cases in which biopsy was done by histologic evidence of testicular atrophy and degeneration. The diagnosis was further supported by a specific response to a therapeutic test with testosterone propionate in all 20 patients so treated.

A clearcut differentiation of the male climacteric from psychogenic impotence was made by assays of urinary gonadotropin, which was decidedly elevated with the former condition and normal with the latter. A simple therapeutic test is helpful in distinguishing between these two conditions.

The symptoms of the male climacteric are different from those of psychoneurosis and psychogenic impotence. Satisfactory therapeutic results were obtained with intramuscular injections of testosterone propionate and with implantation of pellets of testosterone but not with oral or sublingual administration of methyl testosterone.

Although the male climacteric may occur as early as the third decade, it is a relatively rare syndrome, probably affecting only a small proportion of men who live to old age.

ANEURYSM AND URINARY SYMPTOMS

Lazarus and Marks⁵⁰ state that aneurysms of the abdominal aorta can, and frequently do, give rise to urinary symptoms, which may be so predominating as to mask completely those produced by the aneurysm. In most of the reported cases the condition has been mistaken for nephrolithiasis, perinephric abscess or hydronephrosis. The most frequent roentgenographic findings suggestive of aneurysm are renal or ureteral displacement and erosion of bone. Lateral roentgenograms are invaluable in demonstrating these conditions. The outstanding symptom of aneurysm of the abdominal aorta is severe pain.

49. Heller, C. G., and Myers, G. B.: The Male Climacteric: Its Symptomatology, Diagnosis and Treatment. *J. A. M. A.* 126:472-477 (Oct. 21) 1944.

50. Lazarus, J. A., and Marks, M. S.: Aneurysm of the Abdominal Aorta Associated with Urinary Symptoms. *J. Urol.* 52:115-125 (Aug.) 1944.

frequently simulating renal colic, which does not respond to the usual remedial measures and is aggravated by postural changes. Pain is usually due to erosion of bone and pressure on nerve roots. True renal pain may exist, however, in which event it is due to interference with renal drainage or to renal infarction or to both.

Since the two outstanding causes of aneurysm of the abdominal aorta are syphilis and atherosclerosis, routine Wassermann tests on the blood of all patients should be made and anteroposterior and lateral roentgenograms carefully searched for calcareous shadows adjacent to the renal silhouette.

Dissecting aneurysms are most likely to give rise to severe renal symptoms. Renal exploration, particularly when performed on the left kidney, should always include thorough inspection of the renal pedicle. Any suspicious tumefaction in the renal fossa, especially when presenting a bluish discoloration, should never be incised before its true nature is ascertained by aspiration and palpation for thrill. Treatment directed to the relief of renal symptoms resulting from aneurysms of the abdominal aorta should be conservative.

Lazarus and Marks report a case of aneurysm of the abdominal aorta of atherosclerotic origin with urologic symptoms in which the aneurysmal sac, although misinterpreted on the roentgenogram, was clearly recognized at operation and on subsequent roentgenograms.

ROENTGENOLOGIC ASPECTS OF UROLOGY

Arens⁵¹ discusses the roentgenologic aspect of the urologic problem. He states that proper and adequate preparation of the gastrointestinal tract is a prerequisite to satisfactory roentgenographic examination of the urinary tract. An ideal roentgenogram of the urinary tract is one which shows the details, including the outlines of the kidneys. The kidneys are too often obscured by material in the gastrointestinal tract, which may be so dense as completely to vitiate shadows due to stone.

Failure to visualize a urinary calculus on films of the kidney, ureter and bladder does not signify that a stone may not be present. There are radiolucent calculi that cast no shadow. Even a large calcific ureteral stone may not register a shadow on the film when it lies over the ala of

the sacrum. A scout film of the urinary tract usually only the first step in a proper roentgenographic examination.

There is no controversy between excretory urography and retrograde pyelography. Examination by either one method or the other, with a scout film or with all three combined, may be necessary before a satisfactory result can be obtained. It is as important to visualize the normal renal pelvis as the pelvis of the suspected kidney.

A suspected shadow of stone, apparently in contact with a catheter in the roentgenogram may prove to be outside the ureter or the kidney when rotation films are made. Shadows of stone in the right upper quadrant and with the outline of the kidney should not be judged too hastily. They may prove to be gallstone.

Absence of excretion (excretory urography) from one kidney does not necessarily mean "dead kidney." A small stone in the ureter may produce calculous anuria, even though the stone may not be visualized. It has been noted that renal function was restored within five minutes after a ureteral calculus was passed into the bladder.

With reasonable precaution, excretory urography, in experienced and competent hands, is a safe and valuable procedure, and one which frequently gives information obtainable in no other way.

RECTOURINARY FISTULA

Wilhelm⁵² states that rectourinary fistulas due to trauma or acute inflammatory disease frequently heal with conservative treatment. On the other hand, fistulas which are caused by a neoplasm offer a grave prognosis.

Chronic rectovesical and rectourethral fistulas are best approached and repaired by the perineal route. The fistulous opening in the rectum can often be exteriorized and excised with the redundant mucous membrane. If this is not feasible, the freshly sutured defects in the bladder and rectum should be separated by an interposed wedge of the muscle. The rectal sphincter can safely be used for this purpose.

Suprapubic cystostomy is indicated prior to radical reparative operation. On the other hand, preoperative administration of succinylcholine thiazole enabled Wilhelm to abandon preliminary colostomy as a routine measure.

51. Arens, R. A.: The Radiologic Aspect of the Urologic Problem, *J. A. M. A.* 126:605-607 (Nov.) 1944.

52. Wilhelm, S. F.: Rectourinary Fistula, *Gynec. & Obst.* 79:427-433 (Oct.) 1944.

ARCHIVES OF SURGERY

VOLUME 50

MARCH 1945

NUMBER 3

COPYRIGHT, 1945, BY THE AMERICAN MEDICAL ASSOCIATION

CHRONIC THYROIDITIS AND PRIMARY THYROTOXICOSIS (EXOPHTHALMIC GOITER)

KAZIM I. GÜRKAN, M.D.

Professor of Surgery, Istanbul University; Surgeon, the Gureba Hospital

ISTANBUL, TURKEY

TRANSLATED BY PERIHAN CAMBEL, M.D.*

At the present time the different clinical manifestations produced by various pathologic changes in the thyroid gland cannot be considered as well defined, standardized diseases the classification of which is beyond all criticism. Observations recorded in the modern literature on the various kinds of inflammation and dysfunction of this gland are varied and do not always necessarily correspond clinically and anatomically. These diverse observations oppose at times the attempt to classify the pathologic conditions of the thyroid gland. So it is the purpose of this paper to present a peculiar case of chronic thyroiditis which does not seem to fit the generally known description.

HISTORICAL REVIEW

In 1896 Riedel¹ reported a disease which until then had been unknown, a new form of "inflammatory condition in which fibrosis eventually dominates the picture" (Joll²). The patient, a man aged 40, had shown the symptoms of life-threatening dysphonia and asphyxia, hoarseness and a hard, immovable, painless, enlarged thyroid gland. Riedel's clinical diagnosis had been cancer. Extensive adhesions of the gland to the surrounding parts obliged him to abandon resection and resort to excision of a small portion. Microscopic examination revealed chronic inflammation. Riedel called the new condition "iron-hard goitre." His observations on a second case, a year later, induced him to define closely this new term. In 1897 he presented a third case. According to Joll,² the well known English authority on diseases of the thyroid, Bowlby reported a case (1884) in which a condition identical with Riedel's disease was observed at autopsy; but "Riedel's description of the condi-

tion, in 1896, led to its recognition as a clinical and pathological entity."

Cordua was the second to demonstrate the same histologic structure in a thyroid gland, on which he could not perform resection because of too extensive adhesions. In 1898 Tailhefer, of Toulouse, operated in a case in which the clinical manifestations were similar to those in Riedel's cases; he examined microscopically the excised thyroid tissue, corresponded with Riedel about the case and published a report of it. It was the first case of Riedel's disease observed in France. New cases were added to the world literature, and new authors compared histologic and clinical observations; terms like *inflammation chronique primitive cancéroforme* (Tailhefer), *thyroïdite liguense* (Delore and Alamartine) and benign granuloma of the thyroid (Ewing³) were introduced.

Riedel concluded that chronic thyroiditis was the result of an infection with an unknown agent, which spread by the hematogenous or lymphogenous route to the thyroid. Tailhefer expressed the opinion that the agent was *Staphylococcus albus*. Evidence of tuberculosis or syphilis could not be adduced. In spite of the nonspecific structure of the inflammatory lesions, some authors did not dismiss the possibility of tuberculosis as an etiologic factor, stating that this disease may produce nonspecific inflammatory lesions in glandular organs (Wegelin⁴). Reist⁵ and von Werdt⁶ stated the belief that iodine was a causative agent. The inflammatory reaction, however, observed in iodine-treated exophthalmic goiters (colloid stage) does not

3. Ewing, J.: *Neoplastic Diseases*, Philadelphia, W. B. Saunders Company, 1934.

4. Wegelin, C., in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1926.

5. Reist, A.: *Frankfurt. Ztschr. f. Path.* 28:141, 1922.

6. von Werdt, F.: *Frankfurt. Ztschr. f. Path.* 7:461, 1911; cited by Reist.⁵

* From the Second Department of Surgery, Istanbul University.

1. Riedel, 1896, cited by Reist.⁵

2. Joll, C. A.: *Diseases of the Thyroid Gland*, London, William Heinemann, Ltd., 1932.

correspond to the morphologic changes associated with Riedel's disease. The histologic changes observed by Orywall⁷ in the thyroids of iodine-fed mice also cannot be compared with the structure of Riedel's goiter; in the former there were simply slight alterations in the epithelial cells and the colloidal content and a slight increase of connective tissue.

The results of the partly comparative studies of acute, subacute and chronic inflammatory processes of the thyroid prove that Riedel's goiter is a chronic thyroiditis, with a typical clinical course and a typical histologic structure. Microscopically, an increase of the connective tissue, reaching the most extreme degree, and a dense interlobar and intralobar inflammatory infiltration with lymphocytes, plasma cells and mononuclear cells are observed. Lymph follicles, which, according to Joll, are characteristic only of lymphadenoid goiter, may be encountered. The glandular vesicles are greatly affected and damaged by the inflammatory process. On the whole, Riedel's goiter was differentiated clinically and histologically from the acute and subacute inflammations, from lymphadenoid goiter and Simmonds' atrophy. Wegelin, de Quervain, Reist, Simmonds, Hashimoto and Joll established the modern differential diagnosis of the various inflammatory conditions of the thyroid. Weyeneth⁸ contributed the newest and most comprehensive publications in this field, including reports of his own cases and a critical review of the world literature.

Opposing the upholders of these concepts are the so-called unitarians (Ewing, Vaux and others), who do not differentiate Riedel's goiter (chronic thyroiditis) and Hashimoto's struma (struma lymphomatosa). On the other hand, Graham, MacCullagh, Joll, Polowe⁹ and others stated the belief that lymphadenoid goiter is observed only in certain countries, such as Japan, India, England and North America. Recently 8 new cases were added by Weyeneth and Chaval, all of which came from the Swiss Canton of Geneva.

Chronic thyroiditis per se is rare in practically all countries. In 1941 de Quervain¹⁰ expressed the opinion that the condition is still unknown to some pathologists on the European continent.

7. Orywall, W.: *Virchows Arch. f. path. Anat.* 287:348, 1932.

8. Weyeneth, R.: (a) *Arch. f. klin. Chir.* 201:457, 1941; (b) *Rev. méd. de la Suisse Rom.* 63:681, 1943.

9. Polowe, D.: *Struma Lymphomatosa* (Hashimoto) Associated with Hyperthyroidism: Report of Case with Clinical and Histopathologic Study, *Arch. Surg.* 29:768 (Nov.) 1934.

10. de Quervain, F.: *Die Struma maligna*, Stuttgart, Ferdinand Enke, 1941.

Even today cases may be referred to the surgeon in which the clinical diagnosis of cancer of the thyroid has been made. In other cases reliable pathologists may mistake the polymorphic proliferative changes in the epithelium for signs of malignancy (McClintock and Wright¹¹). Everywhere, chronic thyroiditis is rare in Turkey. Cambel¹² reported a case of pemphigus with chronic thyroiditis observed at autopsy. In other cases have been reported in Turkey as far as I know.



Fig. 1.—Patient (A) before and (B) after thyroidectomy.

REPORT OF A CASE

F. E., a merchant aged 56, born in Odemis (Atolia), had lived in Istanbul, Edirne and various other places in Turkey. The patient was admitted to hospital on Oct. 5, 1942 for swelling of the neck, ophthalmos, hoarseness, dyspnea, loss of weight, sleeplessness (fig. 1A). The first symptoms, which appeared one or two years before, consisted of severe diarrhea, continuous nervousness, loss of weight, sleeplessness and tremor of the hands and legs. The patient had weighed 72 Kg., but his weight was reduced to 44 Kg. After treatment for rheumatism and heart disease, he gained 16 Kg. In 1942 the symptoms reappeared. The diagnosis made in the military Ma Hospital and in the university clinic for therapeutic (Prof. Dr. Akil Muhtar Ozden) was exophthalmic goiter. In the clinic the basal metabolic rate

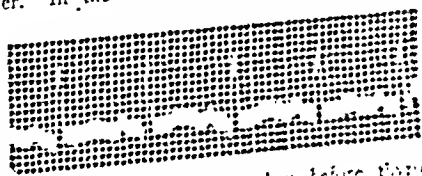


Fig. 2.—Electrocardiogram taken before thyroidectomy.

+76 at the first and +87 at the second examination. The electrocardiogram (fig. 2) showed changes typical of exophthalmic goiter. A disturbance of the increasing prurigo caused the patient to scratch himself with a knife and finally to discontinue treatment.

Examination.—A scarcely palpable, hard, diffuse enlarged thyroid gland was found on Oct. 12, 1942.

11. McClintock, J. C., and Wright, A. V.: *Surg.* 106:32, 1937.

12. Cambel, P.: *Dermatologia* 2:127, 1941.

... was more pronounced on the right side of the neck. Exophthalmos and positive Stellwag and Mobius signs were noted. The pulse rate was 130 and the basal metabolic rate +80. The patient was 1.67 m. tall and weighed 53 Kg. A roentgenogram showed dilatation of the left side of the heart. Chemical examination of the urine and the blood cell count showed nothing. The diarrhea disappeared, but the sleeplessness continued.

of the thyroid to the joining tissues, an almost total thyroidectomy was performed.

Pathologic Report.—The report of the pathologist, Dr. Perihan Cambel, was as follows:

Gross Examination: The surgical specimen consisted of two well encapsulated lobes of the thyroid, weighing 40 Gm. and showing the areas of resection. The capsule was conspicuous but not noticeably thickened. The cut surfaces of the thyroid were light brownish and

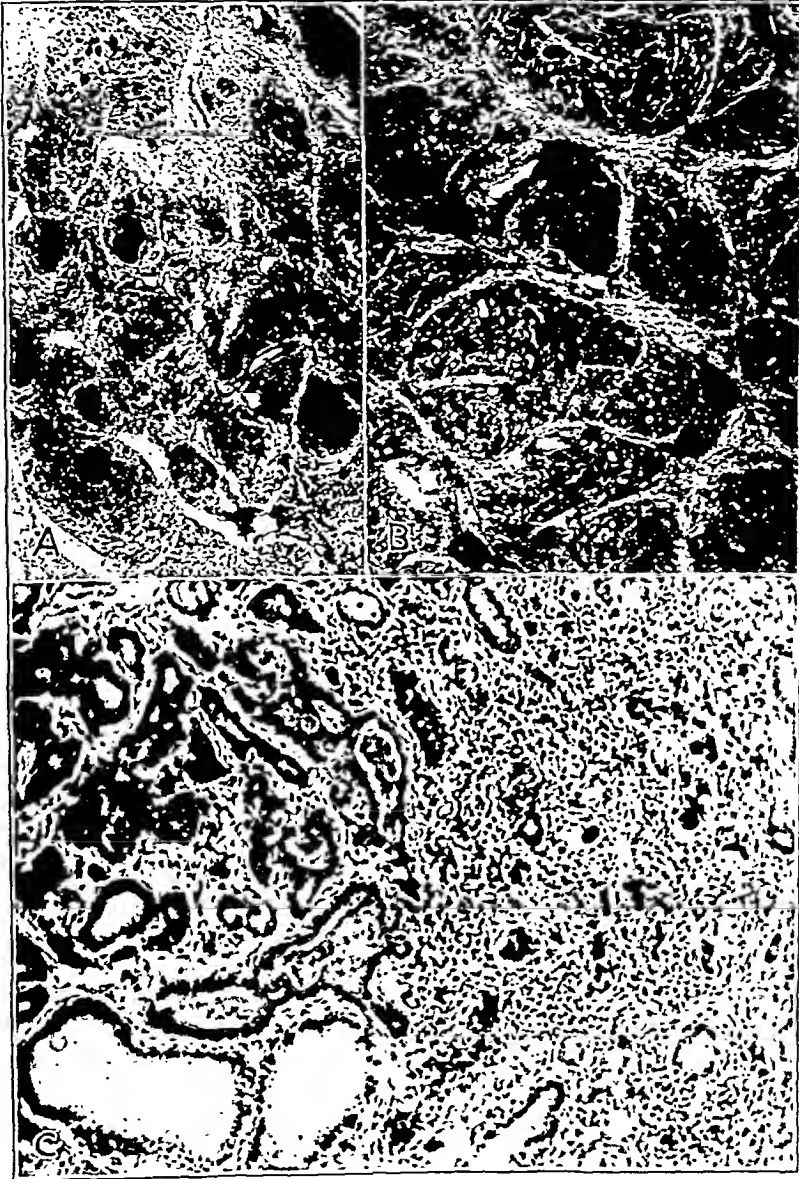


Fig. 3.—Photomicrographs: *A*, chronic inflammatory infiltration, with the formation of lymph follicles partly replacing thyroid tissue. *B*, slighter inflammatory infiltration, showing acini with decreased colloid content. *C*, interlobar inflammatory infiltration, intra-acinary cellular proliferation and liquefaction of colloid matter. Extensive lymphocytic infiltration separates remnants of thyroid tissue. Acini show a lining of cylindric epithelium.

The clinical diagnosis was cancer of the thyroid.

Operation.—Operation was performed on Oct. 10, 1942, with the area under local anesthesia induced with a 0.5 per cent solution of procaine hydrochloride (Prof. Dr. Kazım Gürkan). In spite of extensive adhesions

homogeneous. The thyroid tissue was divided by white connective tissue bands into small lobules.

Microscopic Examination: The lobules of the thyroid gland were separated from one another by thickened, collagenous connective tissue bands and were

sometimes subdivided into smaller lobules, which appeared rather cirrhotic. Some of the acini were separated from one another by intralobar connective tissue and dense lymphocytic and plasmocytic infiltrations. The epithelial lining was cuboid in some places, cylindrical in some and polymorphic in others. The glandular vesicles contained some slightly basophilic, but mostly eosinophilic, colloid which was for the most part liquefied or vacuolated. In some places desquamated cells were seen. In some lobules, as well as in some interlobar connective tissue bands, lymphocytic aggregations formed follicle-like structures. These might contain remnants of thyroid tissue. In areas of denser inflammatory infiltration were observed epithelial polymorphism and intra-acinar cell proliferation (partly polymorphic), which filled the smaller thyroid vesicles. The arteries and veins of the thyroid did not present any unusual changes.

The histologic diagnosis was chronic thyroiditis (fig. 3).

Course.—The wound healed per primam. The patient had a surprisingly rapid recovery of his general health and an increase in weight. His nervousness, as well as all other symptoms except the exophthalmos, disappeared. Figure 1B shows the patient almost a month after the operation. One and one-half years after the operation I was informed that he was still in good health. Myxedema was not noted.

COMMENT

Before discussing the possible association of chronic thyroiditis and primary thyrotoxicosis (exophthalmic goiter), I shall review briefly the different forms of inflammation of the thyroid and their relation to thyrotoxicosis.

1. Acute thyroiditis is often accompanied with thyrotoxicosis (de Quervain, Apelt, Breuer, Petenr, Crile, Dunguer, Walko and Hagen). Histologically, morphologically and physiologically the thyroid tissue shows hyperactivity.

2. Subacute ("giant cell") thyroiditis of the de Quervain type, also classified as chronic thyroiditis by Vaux,¹³ may be accompanied with thyrotoxicosis. Weyeneth noted slight thyrotoxic symptoms in 3 cases. Vaux, who, as a unitarian, classified subacute and chronic forms under the same heading and stated that the various forms of subacute and chronic thyroiditis described by continental authors were different stages of the same disease, found slight degrees of thyrotoxicosis in 9 of 38 cases. In 14 cases she noticed myxedema.

3. Lymphadenoid goiter usually causes myxedema (in 50 per cent of the cases according to American authors and in 2 of 8 cases according to Weyeneth).

4. With Simmonds' fibrous atrophy of the thyroid no thyrotoxic symptoms are observed.

5. The classic symptoms of primary thyrotoxicosis (exophthalmic goiter) associated with

chronic thyroiditis were described for the first time in 1915 by Brünger.¹⁴ Unfortunately, has been impossible to obtain a copy of the author's original article. Brünger observed 2 female patients histologic evidence of chronic thyroiditis. Neither of the patients survived operation.

Simmonds¹⁵ expressed disagreement with Brünger's conception. He stated that there was no relation between exophthalmic goiter and chronic thyroiditis. Wegelin, who stated the belief that the occurrence of thyrotoxicosis in association with acute thyroiditis was almost classic, did not exactly object to Brünger's conception but stated that the association was exceptional. Giovanola¹⁶ also denied a relation between the two conditions. More recently Kreuzbauer,¹⁷ McClintock, Lee¹⁸ and Weyeneth¹⁹ noted thyrotoxic symptoms, such as loss of weight, tremor, increase of the basal metabolic rate to +25 and +45 and slight nervousness, in cases of chronic thyroiditis. In a statistical examination of the cases observed in de Quervain's clinic (1918-1933), Wallis¹⁹ found 100 cases of chronic thyroiditis among 4,148 in which operation was performed on the thyroid. In 15 of these cases there were thyrotoxic symptoms, such as slight or pronounced exophthalmos, tremor and palpitation; loss of weight was noted in 1 instance. Urban²⁰ noted 1 case of chronic thyroiditis among 4,250 cases in which the thyroid gland was examined. Enderlen²⁰ observed 1 case among 3,296 cases in which the thyroid was examined. Neither of them observed any signs of exophthalmic goiter.

Shaw and Smith found 48 cases of chronic thyroiditis among 10,500 cases in which thyroidectomy was performed at the Mayo Clinic. Among these, together with their personal cases, a total of 71 cases of chronic thyroiditis, they could not find a single instance in which there were symptoms of primary thyrotoxicosis.

Austen, Oehler and Bruck stated that in some cases of chronic thyroiditis thyrotoxic symptoms may be observed.

14. Brünger, H.: Mitt. a. d. Grenzgeb. d. Med. u. Chir. 28:213, 1914; cited by Reist¹⁵ and by Giovanola¹⁶.

15. Simmonds, M.: Virchow's Arch. f. path. Anat. 246:140, 1923.

16. Giovanola, C.: Contribution à l'étude de la thyroïdite chronique, Thesis, Lausanne, Imp. B. 1930.

17. Kreuzbauer, F. H.: Arch. f. klin. Chir. 164:178, 1931.

18. Lee, J. G.: Chronic Nontoxic Thyroiditis. Arch. Surg. 31:932 (Dec.) 1923.

19. Wallis, A. E.: Chronic Thyroiditis: A Statistical Analysis of One Hundred Cases. Arch. Surg. 33:545 (Oct.) 1926.

20. Cited by Weyeneth¹⁹.

13. Vaux, D. M.: J. Path. & Bact. 46:441, 1933.

Weyeneth²¹ mentioned that lymphadenoid goiter may show initial signs of thyrotoxicosis (in 50 per cent of his cases), which may be taken as *Basedow frustæ*, but that Hashimoto's struma never causes the symptoms of a fully developed exophthalmic goiter. The same author,²¹ in a personal communication, stated that in carefully examined material in cases of various types of chronic thyroiditis he had not observed a case of primary thyrotoxicosis.

Although several authors observed symptoms of a hyperfunctioning thyroid, Brüngrer was the only one before me to note primary thyrotoxicosis (exophthalmic goiter), with its cardinal symptoms, associated with chronic thyroiditis. On the other hand, the majority of authors stated that there is no relation between the two conditions. The case presented in this paper throws new light on the problem. Histologic examination showed undeniably morphologic evidences of chronic thyroiditis combined with signs of

hyperfunction, which persisted in spite of the intake of large doses of iodine. Clinically the presence of exophthalmic goiter, with its cardinal and other symptoms, was just as certain. The symptoms consisted of an increase in the basal metabolic rate to +87 per cent, pronounced exophthalmos, tremor, sinus tachycardia, loss of weight and attacks of diarrhea. This case demonstrates undeniably the association of the two conditions.

SUMMARY

In the first operative case of chronic thyroiditis observed in Turkey the cardinal and other symptoms of primary thyrotoxicosis (exophthalmic goiter) were clinically apparent. The diagnosis of the pathologist, Dr. Perihan Cambel, was chronic thyroiditis with histologic signs of hyperfunction of the thyroid. A review of the literature and the present case indicates that the association, even if rare, of histologically evident chronic thyroiditis and a fully developed exophthalmic goiter does exist.

Istanbul University.

21. Weyeneth, R.: Personal communication to the author, 1943.

CONTINUOUS SPINAL ANESTHESIA

OBSERVATIONS ON 1,200 PATIENTS

R. C. MARTIN, M.D.; H. LIVINGSTONE, M.D., AND V. WELLMAN, M.D.

CHICAGO

Continuous, fractional or serial spinal anesthesia, since its introduction by Lemmon¹ on April 10, 1939, has been discussed in several publications, including, among others, those of Popova,² Nicholson,³ Tuohy,⁴ Hand and Schuhmacher,⁵ Leigh and Burford,⁶ Haugen, Ruth and Taylor,⁷ Ansbro and Pico,⁸ Lundy and his associates,⁹ Appgar,¹⁰ Fraser,¹¹ Hale and Shaar¹² and Lemmon and Hager.¹³

The interest in and the usefulness of this type of anesthesia have prompted us to report a series of 1,200 patients on whom operation was performed during continuous spinal anesthesia. A complete study, including adequate postoperative observations, has been made on the first 563 consecutive patients.

From the Department of Surgery, the University of Chicago.

1. Lemmon, W. T.: A Method for Continuous Spinal Anesthesia, *Ann. Surg.* **111**:141-144 (Jan.) 1940.
2. Popova, A. F.: Experimental Studies on Fractional Lumbar Anesthesia, *Vestnik khir.* **59**:101-108 (Jan.) 1940.
3. Nicholson, M. J.: Continuous Spinal Anesthesia, *Lahey Clin. Bull.* **2**:34-37 (Oct.) 1940.
4. Tuohy, E. B.: Continuous Spinal Anesthesia. *Proc. Staff Meet., Mayo Clin.* **16**:257-259 (April 23) 1941; Continuous Spinal Anesthesia: Its Usefulness and Technic Involved, *Anesthesiology* **5**:142-148 (March) 1944.
5. Hand, L. V., and Schuhmacher, L. F.: Pontocaine-Glucose Solution for Fractional Spinal Anesthesia, *Lahey Clin. Bull.* **2**:167-173 (Oct.) 1941.
6. Leigh, H., and Burford, G. E.: Simplified Equipment for Continuous Spinal Anesthesia, *Anesth. & Analg.* **20**:358-359 (Nov.-Dec.) 1941.
7. Haugen, F. P.; Ruth, H. S., and Taylor, I. B.: Serial Spinal Anesthesia, *Anesthesiology* **3**:52-60 (Jan.) 1942.
8. Ansbro, F. P., and Pico, L. J.: Continuous Spinal Anesthesia, *Am. J. Surg.* **55**:504-508 (March) 1942.
9. Lundy, J. S.; Tuohy, E. B.; Adams, R. C.; Mousel, L. H., and Seldon, T. H.: Annual Report for 1941 of the Section on Anesthesia, *Proc. Staff Meet., Mayo Clin.* **17**:225-238 (April 15) 1942.
10. Appgar, V.: Continuous Spinal Anesthesia, *Anesthesiology* **3**:522-529 (Sept.) 1942.
11. Fraser, R. J.: Continuous Lumbar Anesthesia, *Anesth. & Analg.* **22**:38-45 (Jan.-Feb.) 1943.
12. Hale, D. E., and Shaar, C. M.: Continuous Spinal Anesthesia, *Anesthesiology* **5**:53-60 (Jan.) 1944.
13. Lemmon, W. T., and Hager, H. G.: Continuous Spinal Anesthesia: Observations on Two Thousand Cases, *Ann. Surg.* **120**:129-142 (Aug.) 1944.

Procaine hydrochloride was employed as the anesthetic agent in this series, since, as Lemmon pointed out, its relative toxicity is less than that of metycaine hydrochloride, tetracaine hydrochloride or nupercaine hydrochloride. Procaine hydrochloride both as a 10 per cent solution and as crystals was used, and no difference in effectiveness between the two preparations was noted. The procaine was dissolved in the patient's spinal fluid, making a 5 per cent solution. Occasionally additional doses consisted of procaine hydrochloride dissolved in sterile isotonic solution of sodium chloride or distilled water to make a 5 per cent solution.

A brief review of our method of management follows:

METHOD OF MANAGEMENT

Premedication.—Calcium pentobarbital and morphine were given one to one and one-half hours before operation. The average adult who was considered a fair, good risk received calcium pentobarbital in doses of from 0.18 to 0.27 Gm. in 50 cc. of water through the rectum if no pathologic condition of the rectum was present, and 0.01 Gm. of morphine sulfate was given by hypodermic injection. This dose was decreased for the aged, extremely ill and other patients considered poor risks. Subsequent injections of morphine were administered subcutaneously or intravenously, when indicated, during long operative procedures.

Technic.—The patient was placed on a rubber-covered mattress (figure), which is 6 feet (183 cm.) long, 18 inches (46 cm.) wide and 5 inches (13 cm.) thick. The mattress has a cutout area, 7 inches (18 cm.) in length and 6 inches (15 cm.) in width, that fits under the lumbar portion of the spine when the patient is supine. This mattress is constructed in sections for use when the patient is in various positions. Extra long metal holders for shoulder braces are needed because of the thickness of the mattress. Shoulder braces are essential to prevent displacement of the spinal needle when some degree of the Trendelenburg position is employed to obtain a high block. The patient was placed in the left lateral decubitus position for the lumbar puncture. With aseptic technic, a 1 per cent solution of procaine hydrochloride and ephedrine sulfate was injected locally over either the second or the third lumbar interspace. Nine patients in this series received no ephedrine because of extreme hypertension. For patients with a blood pressure of 180 mm. of mercury or more, ephedrine was omitted entirely, or a solution containing 0.024 to 0.048 Gm. of ephedrine sulfate was given intramuscularly after the lumbar puncture had been made and just before the procaine solution was injected. Such patients frequently have a labile blood pressure, which may fall

to 130 mm. of mercury when no ephedrine is given. The average patient received 0.049 Gm. of ephedrine sulfate. If hypotension was present after the initial administration of ephedrine, the dose was repeated before the spinal injection was made.

A Sise introducer was used to puncture the skin and make a point of entrance for the malleable German silver spinal needle. Such needles are made in three sizes: 17, 18 and 19 gage; they vary in length from $3\frac{1}{2}$ to 4 inches (9 to 10 cm.). It is advisable to use as short a needle as possible in order to decrease the likelihood of its displacement when the patient is turned. On the other hand, for extremely obese patients the longest needle is necessary, and even then there may be displacement outward by the excess soft tissues when the patient is placed supine. When a successful lumbar puncture had been made, a 10 cc. Luer-Lok syringe was connected with the hub of the needle. From the average patient undergoing a long surgical procedure 4 cc. of spinal fluid was withdrawn in a first syringe, 4 cc. in a second syringe and 2 cc. in a third syringe. Equal parts of 10 per cent solution of procaine hydrochloride and spinal fluid were mixed, giving a 5 per cent solution of the drug, each cubic centimeter of which contained 50 mg. of procaine hydrochloride. When crystals were employed, 2 cc. of

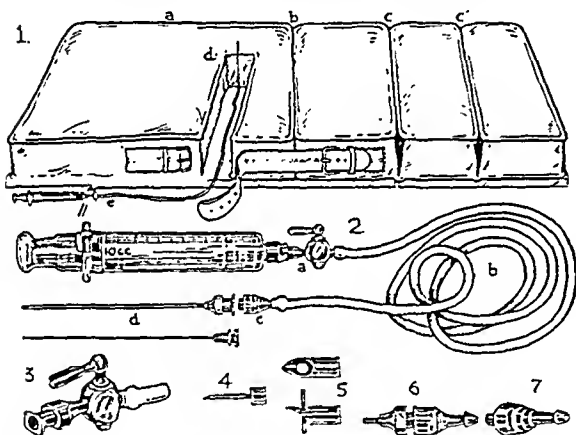
dition, the length of the spine and the height of anesthesia required; a slower rate is advisable for a patient who is considered a poor risk or for low block. A larger initial dose was employed only for extremely obese persons or for patients with gross deformity of the spinal column with which the hazard of displacement of the needle during changes in position was great. The initial injection never exceeded 1.5 mg. of procaine hydrochloride per pound (0.5 Kg.) of body weight, and usually it was 1 mg. or less per pound of body weight. Some authors have reported the use of a smaller initial dose. Since intra-abdominal relaxation was necessary for most of the patients in this series, an initial dose sufficient for exploration was provided.

Two assistants turned the patient from the lateral to the supine position, while the anesthetist held the syringe and tubing and directed the turning so that the needle was not displaced and lay free in the space provided in the mattress. The assistants slipped their hands under the patient's shoulders and hips, lifted him to the left edge of the table and then gently turned him to the supine position, making sure that the spine was not twisted at any time. Shoulder braces were used; the needle was watched when the Trendelenburg position was established, and the table was kept on a straight plane at all times to prevent dislocation of the spinal needle. The syringe was secured with a butterfly adhesive tape a few inches to the right of the patient's head.

The blood pressure, pulse rate and respiratory rate were recorded every five minutes. The table was kept flat for five minutes after the injection. If the level of anesthesia obtained was not high enough at the end of this time the table was placed in varying degrees of the Trendelenburg position until the desired level was reached. An additional 1 cc. (50 mg. of procaine hydrochloride) of the procaine-spinal fluid solution was injected rapidly if the block was not high enough at the end of ten minutes. We did not employ barbotage, since this method makes it impossible to calculate the concentration of the remaining solution, as well as the level of anesthesia. The average patient required additional injections of 50 mg. each at the end of approximately the first hour and usually every thirty minutes thereafter.

The underlying principles of spinal anesthesia must be observed throughout the procedure if the administration of continuous spinal anesthesia is to be successful. Dispersion, convection and diffusion must be considered when anesthetic solutions are injected into the subarachnoid space. The relation of the specific gravity of the solution to the spinal fluid is important. A 5 per cent solution of procaine hydrochloride and spinal fluid is hyperbaric, having a specific gravity of 1.015, as compared with 1.007 for the spinal fluid. The position of the patient during the first ten to fifteen minutes after the anesthetic solution is injected must be carefully controlled in order to localize the block correctly. The height of anesthesia can also be affected by the site of injection, the length and caliber of the patient's spinal canal and the rate of injection of the anesthetic solution. Since additive amounts of the drug are usually only 1 cc. in volume, this small quantity will not give a high block unless the rate of injection is rapid and the patient is in the proper position.

It must also be remembered that the sensory roots are more susceptible to the anesthetic solution than are the motor roots. Since the sensory root fibers are blocked in the following sequence, i. e., fibers carrying pain, touch, temperature and muscle sense and, finally, visceral sensory fibers from the sympathetic system, it seems reasonable to assume that unpleasant sensations or actual pain which are occasionally produced by traction on the viscera are probably due to the unparalyzed sympathetic pathways. In such a situation supply-



Equipment used for continuous spinal anesthesia (reproduced with the permission of Dr. William T. Lemon). 1, table pad in sections (a, b, c, c'), with illustrations of the position of the spinal needle (d), the tubing (e), the stopcock and the syringe. 2, Luer-Lok syringe connected to the stopcock (a), the rubber tubing (b), the Luer-Lok connection (c) and the spinal needle (d). 3, close-up view of the stopcock. 4, needle introducer for puncturing the skin. 5, short bevel and counter opening in the lumbar puncture needle. 6, plug for the spinal needle, to prevent loss of cerebrospinal fluid. 7, Luer-Lok plug.

spinal fluid was used to dissolve each 100 mg. of crystals. The syringe was then attached by means of a stopcock to 30 inches (76 cm.) of thick-walled, small bore rubber tubing. The stopcock was opened; the tubing was held above the level of the syringe, and 2 cc. of the mixture was forced into the tubing to displace air completely and fill the lumen. The stopcock was then closed, and the Luer-Lok connection on the distal end of the tubing was connected with the spinal needle. Since the operations in the present series were all major surgical procedures, mainly laparotomies, the average initial dose was 150 mg. of procaine hydrochloride (3 cc.), injected at the rate of about 0.5 cc. per second. Judgment must be used in determining the rate of injection for the individual patient, which should depend on the patient's general con-

mentary gas anesthesia and adequate oxygenation usually control the situation. If pentothal sodium is given intravenously, it should be administered in only minute amounts, just sufficient to keep the patient drowsy and euphoric. Inhalations of oxygen should be given at the same time. Administration of pentothal sodium sufficient to produce unconsciousness introduces the additional hazard of regurgitation and aspiration during surgical procedures on the upper portion of the abdomen.

A fall in blood pressure is frequently followed by nausea or vomiting, due to lack of oxygenation of the vomiting center. It is therefore of greatest importance to ascertain promptly any evidence of anoxia, such as occurs with a high intercostal block or fall in blood pressure, and to begin oxygen inhalation immediately before disturbing manifestations, such as nausea or vomiting, occur.

Postoperative Care.—The patient was kept flat in bed without a pillow for twenty-four hours. During the past year early rising has been practiced in two surgical services, in which all patients who are able are urged to become ambulatory twenty-four to forty-eight hours after operation. So far, there have been no disturbing manifestations, such as headache, from this practice.

After operation the blood pressure, pulse rate and respiratory rate were recorded every fifteen minutes for two hours and thereafter at longer intervals, if indicated. Oxygen therapy was administered to any patient having evidence of surgical shock from massive intra-abdominal resection or hemorrhage.

COMMENT

Since the University of Chicago is a teaching institution and surgery interns, as well as anesthesia residents, are being trained, spinal anesthesia was administered to the first 563 patients by a total of twenty-seven persons. This factor should be considered in evaluation of the results.

Age.—The age of the first 563 patients varied from 18 to 86 years, with 276 in the 40 to 60 year group. Thirty-three patients were from 70 to 79 years old, and 3 were over 80 years of age. Approximately 17 per cent of these patients were considered as poor or serious risks for operation, while 41 per cent were only fair surgical risks.

Preoperative Complications.—Hypertension, arteriosclerosis, heart disease of various types, anemias of varying severity, jaundice, serious debility, marked obesity, diabetes mellitus and pulmonary tuberculosis made up the bulk of the preoperative complications. Four patients had pernicious anemia and 3 had latent syphilis. While several of these conditions are considered by many persons as contraindications to spinal anesthesia, in our evaluation of the patients and of the surgical procedures contemplated, spinal anesthesia seemed to us a lesser evil than general anesthesia of the length and depth that would have been required.

Duration and Height of Anesthesia.—The duration of the anesthesia was from one and

one-half to three hours in 72 per cent of the patients. In most instances the level of anesthesia extended as high as the seventh or the fourth dorsal nerve roots. Fifty-two operations, or 9 per cent, lasted from three to four hours; 16, or 4 per cent, from four to five hours, and 4, or 7 per cent, for more than five hours. The longest operative procedure in our series, a total pancreaticectomy, lasted seven hours and forty-five minutes.

TABLE 1.—Total Dose of Procaine Hydrochloride

Time	Minimum, Mg.	Maximum, Mg.	Average, Mg.
Less than 1 hour.....	120	250	154
Less than 1½ hours.....	135	500	297
Less than 2 hours.....	150	500	304
Less than 3 hours.....	200	675	341
Less than 4 hours.....	200	700	425
Less than 5 hours.....	250	1,050	525
Less than 8 hours.....	...	900	...

Dosage.—Table 1 gives the minimum, maximum and average doses of procaine hydrochloride for operations of stated lengths. The initial dose of 150 mg. of procaine hydrochloride is far greater than that used in some clinics and was perhaps excessive for the shorter surgical pro-

TABLE 2.—Types of Operation Performed on 126 Patients Under Continuous Spinal Anesthesia

	First Series of 563 Operations	Total Number Operations
Operations on the biliary tract.....	145	210
Resection of stomach.....	61	125
Other operations on stomach.....	17	42
Repair of diaphragmatic hernia.....	1	1
Repair of incisional hernia (upper abdominal).....	27	55
Exploratory laparotomy and biopsy (inoperable condition).....	15	91
Operations on pancreas, etc.....	15	57
Splenectomy.....	7	154
Intestinal resections, etc.....	72	154
One stage abdominoperineal resection of rectum.....	15	27
Perineal excision of carcinoma of rectum.....	2	2
Appendectomy.....	51	55
Gynecologic operations (intra-abdominal).....	8	55
Operations on kidney, bladder or ureter.....	1	55
Inguinal or femoral herniotomy (many hernias were bilateral; 5 were strangulated).....	24	55
Miscellaneous abdominal resections (retroperitoneal, adrenal, etc.).....	42	47
Operations on lower extremities (excision of aneurysm or large tumor).....	1	7
Total number of operations.....	562	1,200

cedures. However, because of the need for intra-abdominal relaxation in these patients and because of the chance that the needle might dislodge when the patient was turned, we felt that this dose was desirable.

Operative Procedures.—Operation on the biliary tract, gastric resection, exploratory laparotomy and intestinal resection were the operations of greatest frequency. Table 2 pre-

ents the operative procedures for the entire series, as well as for the first 563 patients discussed. The brief headings do not give an accurate picture of the extensive resections done for advanced malignant growths, which made up a relatively large per cent of the total number of operations. For instance, the heading "Operations on pancreas, etc." usually included two or more of the following procedures: gastrectomy, splenectomy, partial hepatectomy, adrenalectomy and various intestinal resections.

Anesthetic Agents.—For 65 per cent of the patients in this series procaine hydrochloride or procaine hydrochloride together with inhalation of oxygen was employed. For the remaining 35 per cent it was necessary to supplement the anesthetic with nitrous oxide and oxygen, ethylene and oxygen or ethylene oxygen and ether; and in a few cases procaine hydrochloride infiltration was employed, or pentothal sodium injected intravenously in 2.5 per cent solution. Nitrous oxide and oxygen were given to 12 per cent of the patients; ethylene and oxygen, to 14 per cent; nitrous oxide and oxygen supplemented with ethylene and oxygen, to 2 per cent; ethylene, oxygen and ether, to 4 per cent, and procaine hydrochloride infiltration or intravenously administered pentothal sodium, to 3 per cent. Supplementary anesthesia was necessary for the comfort of nervous, apprehensive persons and for patients having persistent nausea and emesis during operations on the upper portion of the abdomen, due to traction on the mesentery or in the area of the gallbladder or to manipulation of the stomach. Gas and ether were given to 20 patients (3.5 per cent) because of partial or complete failure of the anesthetic or inadequate relaxation. In some of these patients spinal fluid could be freely withdrawn and injected, but no anesthesia resulted. In the remainder of these patients with unsatisfactory anesthesia, the needle became dislodged when the patient was placed supine or during changes in position during the surgical procedure.

Complications During Anesthesia.—Nausea and emesis were the most frequent complications encountered during anesthesia. They were observed in 17 per cent of the patients; in most instances they occurred during exploration of the upper part of the abdomen and were associated with a fall in blood pressure. Several apprehensive and psychoneurotic persons vomited intermittently during less extensive procedures. The average fall in blood pressure attributable to the anesthetic was 11 mm. of mercury and occurred five to fifteen minutes after the initial injection. Subsequent fall in blood pressure

occurred in a number of patients when the peritoneum was opened and exploration was begun. This effect is comparable to that observed during similar manipulations under inhalation agents. In 6 per cent of the patients the blood pressure fell to shock levels during vigorous exploration of the upper portion of the abdomen. Inhalation of oxygen and subcutaneous or intravenous injections of ephedrine sulfate, the choice depending on the extent of the drop, were administered for the fall in blood pressure due to the exploration, and satisfactory results were obtained. Blood or plasma was used to combat a decrease in blood pressure due to hemorrhage. As much as 4,000 cc. of whole blood was given during a single operation.

Pain in the shoulders was severe and persistent in a few patients during manipulation in the area of the gallbladder.

Complete paralysis of the intercostal muscles due to a high block occurred in 1 patient. Recovery was uneventful after the use of oxygen inhalations and ephedrine.

Postoperative Complications.—Postoperative nausea and emesis occurred in 7 per cent of the patients of this series. While these complications were usually of brief duration, they sometimes persisted for two or three days, until medication with opiates was discontinued. Distention was present in 2.7 per cent. Impaired hepatic function, as determined by the level of prothrombin, total proteins, cholesterol and cholesterol esters in the blood, was present in 2.2 per cent of the patients. In each of these patients hepatitis was present at the time of the operation.

Twenty-five patients, or 4.4 per cent, had postoperative pulmonary complications. Five, or 0.9 per cent, had lobar pneumonia, and 12, or 2.1 per cent, bronchopneumonia. Pneumonia developed one to three days after the surgical procedure in several patients, most of whom had been considered poor risks before operation. Atelectasis occurred in 8 patients, or 1.4 per cent.

In only 2 patients was there a postanesthesia fall in blood pressure of any consequence, and in neither of these did the pressure fall to shock levels. From this group we excluded those with postoperative hemorrhages.

The incidence of urinary retention was 4 per cent and that of cystitis 2 per cent. Rarely was retention present more than two to three days.

Eleven patients, or 2 per cent, complained briefly of postoperative backache and 12, or 2.1 per cent, of headache. Some, but not all, of the patients with headache sat up on the day of operation, in spite of careful instructions to remain flat in bed without a pillow for twenty-four hours.

Four days after an "interval appendectomy" in which a normal appendix was removed, a 24 year old woman complained of severe headache and had a positive Kernig sign. These symptoms gradually disappeared, but at the time of her discharge from the hospital, on the tenth postoperative day, there was still cervical pain when she sat up. There was no postoperative fever or elevation of the white cell count. The clinical diagnosis was aseptic meningitis following spinal anesthesia. A rapid and uneventful lumbar puncture had been performed and 150 mg. of procaine hydrochloride in 3 cc. of spinal fluid injected. The level of the anesthesia reached the sixth dorsal nerve root, and the operation lasted only fifteen minutes. Spinal fluid withdrawn before the anesthetic solution was injected contained a few red blood cells and 2 lymphocytes per cubic

was emaciated and nervous and was considered a poor operative risk. A radical resection of the abdominal wall and a portion of the small intestine together with removal of the right kidney was performed in two hours and forty-five minutes. There was considerable hemorrhage. The normal blood pressure was 134 mm. of mercury systolic and 80 mm. diastolic. The blood pressure was not obtainable for thirty minutes two hours after the operation began in spite of liberal parenteral administration of blood and saline solution. While the abdomen was being closed, the blood pressure rose to 110 systolic and 80 diastolic and was at this level when the patient left the operating room. On the eighth postoperative day the wound broke down and became infected with *Bacillus pyocyaneus*. The patient became progressively weaker and died

TABLE 3.—*Death Occurring After Continuous Spinal Anesthesia in 563 Patients*

No.	Deaths, %	Cause of Death	Interval Between Operations and Death						
			Day of Operation	1-3 Days	4-7 Days	7-14 Days	14-21 Days	Within 1 Month	Within 2 Months
6	1.06	Cancer of pancreas.....	2	..	1	1	2
4	0.71	Cancer of stomach.....	..	1	1	..	1	..	1
2	0.35	Cancer of colon.....	1	..	1
1	0.18	Cancer of gallbladder and liver....	1
1	1.2	Pneumonia.....	..	1	2	3	1
1	0.18	Aspiration of vomitus.....	1
5	0.88	Pneumonia.....	..	1	2	2
5	0.8	Pneumonia.....	..	1	1	1
				(broncho- pneumonia)	(lobar pneumonia)				(broncho- pneumonia)
2	0.35	Aspiration of vomitus.....	1	1
2	0.35	Pulmonary embolism.....	1	1	..
2	0.35	Coronary occlusion.....	2
3	0.5	Postoperative hemorrhage.....	..	2
1	0.18	Coronary occlusion.....	1
2	0.35	Postoperative hemorrhage.....	..	1	..	1
1	0.18	Cerebral accident.....	..	1
1	0.18	Hepatorenal failure.....	1
2	0.35	Cardiac failure.....	..	1	..	1
1	0.18	Uremia.....	1
5	8	Total.....	2	10	11	9	6	2	6

millimeter. No. postoperative lumbar puncture was performed.

Deaths.—Table 3 summarizes the postoperative deaths. There were 46 deaths in this series of 563 patients, giving a mortality rate of 8 per cent. Thirty-three of the deaths occurred in patients who had malignant disease. There were no fatalities in the operating room.

Five patients died of hepatic damage, one to fourteen days after operation. The youngest of these patients was a man aged 38 with biliary cirrhosis, who was subjected to an exploratory laparotomy and a choledochenterostomy. He died on the second postoperative day. The remainder of the group were over 50 years of age and had cirrhosis of the liver or hepatitis at the time of operation.

Coronary occlusion occurred on the eighteenth postoperative day in a 51 year old man with recurrent carcinoma of the cecum. The patient

suddenly on the eighteenth postoperative day. Postmortem examination revealed complete occlusion of the anterior descending branch of the left coronary artery with a thrombus.

Circulatory failure occurring three hours after operation accounted for the death of 2 patients. Both patients had extensive malignant lesions, bled profusely and went into surgical shock during a pancreatoduodenectomy and a resection of the stomach respectively.

Two extensive hemorrhages were observed. The first of these occurred twenty-four hours after excision of the gallbladder, the common duct and the hepatic duct in a 59 year old man with carcinoma of the hepatic duct. The second was from the operative wound on the eleventh day in a patient with a large metastatic abdominal tumor.

Peritonitis accounted for the deaths of 7 patients, occurring six to eleven days after opera-

tion. Terminal bronchopneumonia developed in 2 of these patients.

A 64 year old woman with carcinoma of the sigmoid had a cerebral accident three days after drainage of a retrouterine abscess, an end to end anastomosis and a loop colostomy. The patient had generalized arteriosclerosis, a blood pressure of 160 mm. of mercury systolic and 100 mm. diastolic and a history of a cerebral accident in 1938. No rise in blood pressure occurred during the surgical procedure.

Hepatorenal failure on the sixth postoperative day caused the death of a 70 year old woman who had carcinoma of the head of the pancreas with extensive metastases to the liver. An exploratory laparotomy was performed without untoward effects, but heart failure began ten hours after the operation. Digitalization was carried out, and improvement was noted, until the patient became anuric on the third postoperative day.

Cardiac failure was the immediate cause of death of 2 patients. One of these, a 72 year old woman with carcinoma of the rectum, had a preoperative blood pressure of 164 systolic and 80 diastolic, hypoproteinemia (4.54 Gm. of total protein per hundred cubic centimeters of blood) and a history of heart failure ten years previously. The first stage of a combined abdominoperineal resection was performed, with the patient under spinal anesthesia, without deleterious effects. Four days later she was given spinal anesthesia for the second stage. Ten minutes after intraspinal injection of 150 mg. of procaine hydrochloride the patient went into shock. Inhalation of oxygen and intravenous injection of 0.024 Gm. and intramuscular injection of 0.024 Gm. of ephedrine sulfate restored the blood pressure to its former level, and the operation proceeded. Fibrillation began on the afternoon of the operative day. Heart failure began in six days, and she became progressively worse in spite of administration of oxygen and digitalis. Death occurred on the sixteenth day: postmortem examination revealed hydrothorax, pulmonary edema and coronary arteriosclerosis.

The other patient, an emaciated man aged 67, had carcinoma of the head of the pancreas with pleural and hepatic spread. This patient had obstructive jaundice, auricular fibrillation, ascites, secondary anemia, nutritional edema and a massive hydrothorax on the left side. He was dyspneic and gasping for breath before the spinal anesthetic was administered. During a pancreatoduodenectomy and a complete resection of the pancreas, which lasted four hours and forty minutes, 550 mg. of procaine hydrochloride was given. Oxygen was administered throughout the

procedure. The blood pressure fell to 60 mm. of mercury systolic and 40 mm. diastolic twenty minutes after the operation began and remained low throughout. Thirty-seven hundred cubic centimeters of blood and 1,500 cc. of saline solution were given intravenously. Heart failure, with pulmonary edema, oliguria and hyperglycemia, followed. Oxygen was administered. The patient died on the second postoperative day, while a thoracentesis was being performed.

The immediate cause of death of 3 patients was lobar pneumonia or bronchopneumonia. Gastroenterostomy was performed on an emaciated 47 year old man with a stenosing duodenal ulcer and nonspecific ulcerative colitis. Peritonitis developed on the fourth postoperative day and pneumonia on the fifth. The patient died on the sixth postoperative day.

An anemic woman aged 68 with carcinoma of the gallbladder underwent a three hour operation consisting of exploratory laparotomy and excision of a specimen of the tumor for biopsy. Pneumonia developed on the first postoperative day, and death occurred on the third postoperative day.

The third case of pneumonia developed two months after operation and had no relation to the anesthesia.

One death, due to aspiration pneumonia, occurred in an 83 year old man who had a combined abdominoperineal resection for carcinoma of the rectum. Two days after the operation the patient was nauseated and vomited. A cough productive of thick sputum followed this episode. The colostomy became necrotic three days later; so its gangrenous portion was removed and a new colostomy opening established, with the operative area under local anesthesia. The patient sank into a comatose state and died later the same day. Postmortem examination of the lungs revealed areas of leukocytic consolidation with edema. In some places there were gangrenous areas, with little surrounding inflammatory reaction. The bronchioles were filled with an exudate; there was extensive bacterial colonization, and the mucosa was ulcerated.

SUMMARY

The clinical experience gained from employment of continuous spinal anesthesia with 1,200 patients has led to the following impressions and conclusions: Excellent muscular relaxation and prolonged operating time make this type of anesthesia increasingly popular with surgeons. After operation, during the first twelve to twenty-four hours, the patients are generally in better condition than they are after inhalation anesthesia.

of second or third plane depth. They are rational and cooperative and have a minimal amount of the fluid imbalance resulting from nausea, emesis and diaphoresis. Urinary retention and abdominal distention occur frequently. A minimum of nursing care is required, since the patient is awake and relatively comfortable; also, the dangers of respiratory obstruction or of aspiration of vomitus are practically removed.

A wide variation in individual requirements of procaine was noted in this series. One patient was given 1,050 mg. of procaine hydrochloride in five hours, while another required only 900 mg. for an operation lasting seven hours and forty-five minutes. Absence of anesthesia when spinal fluid could be freely withdrawn and re-injected was puzzling in the few cases in which it was noted. No doubt, with a long-beveled needle there is still the possibility of part of the injection being made into the peridural area.

Light supplementary anesthesia, induced with one of the anesthetic gases or with intravenously administered pentothal sodium, was sometimes desirable for the comfort of the patient during a surgical operation on the upper part of the abdomen. This "combined anesthesia" was also valuable for very nervous persons undergoing

long procedures, while the spinal block provided the necessary intra-abdominal relaxation.

A number of patients in this series were candidates for any type of anesthesia or operation. While local anesthesia would have been less hazardous for them than spinal anesthesia, it would not have provided adequate relaxation for the operation that was to be performed.

No residual paresis or paresthesia was in our series, although the spinal needle remained in the subarachnoid space from three to five hours in many instances.

There was a low incidence of anesthesia complications among the 46 persons who died (1.7 per cent) after the first 563 operations. As seen in table 2, the death rate has decreased since the first 563 surgical procedures, owing to increased use of continuous spinal anesthesia for less extensive procedures, such as repair of inguinal and femoral hernias and operation on the lower portion of the abdomen.

The underlying principles of spinal anesthesia must be scrupulously observed throughout any surgical procedure if the method for continuous spinal anesthesia is to be successful.

THROMBOPLASTIC REAGENT

DEVELOPMENT OF A MORE SUITABLE PREPARATION FOR MEASURING
ACCELERATED CLOTTING TENDENCY AND FOR USE FOLLOWING
ADMINISTRATION OF DICOUMARIN (3,3'-METHYLENE-
BIS-[4-HYDROXYCOUMARIN])

CHARLES E. BRAMBEL, PH.D.
BALTIMORE

It is a well established fact that in certain clinical conditions, especially those following surgical procedures and trauma, the equilibrium of the coagulation elements of the blood is shifted to a state favorable to clotting.¹ A laboratory procedure is needed for detecting this tendency to intravascular clotting before the appearance of thrombotic phenomena. If such a procedure were available to the clinician, in vivo anticoagulants, such as heparin or dicoumarin (3,3'-methylene-bis [4-hydroxycoumarin]), could be administered to patients having indications of such a tendency. Serious consequences and long periods of hospitalization could be averted in many instances. The introduction of dicoumarin,² however, has posed another problem, that of maintaining a precise control of the mechanism for blood coagulation in order to avoid

hemorrhagic consequences following the use of this drug. Difficulty in maintaining a given clotting level, as well as undesirable results, including death, has been reported.³

A biochemical approach to the problem of detecting a tendency to intravascular clotting has been developed by two methods of investigating the coagulation reaction: (1) study of the prothrombin activity of serial dilutions of plasma,⁴ and (2) study of thromboplastic activity by observing the effect of heparin on the clotting of whole blood.⁵ With the use of dilute plasma in an adaptation of Quick's procedure, increased prothrombin activity has been demonstrated in the following clinical conditions: thrombophlebitis, post-traumatic, postoperative and postpartum states and gangrene.⁶ The original method, however, gave no clue that it could be used for such a purpose, since Quick employed only normal plasma to construct his prothrombin activity curves. Resistance to intravenous administration of heparin^{7a} has also been reported as an indication of increased coagulability of intracorporeal blood. With the aid of a procedure for testing tolerance to heparin it has been pos-

From the Department of Clinical Biochemistry, Mercy Hospital.

Mrs. Raymond C. Teubner, B.S., M.T., carried out the technical work.

This investigation has been made possible through a grant in aid by the Abbott Laboratories, North Chicago, Ill.

Prof. Alsoph H. Corwin, of the Department of Chemistry, the Johns Hopkins University, and Dr. Karl J. Brunings, of the Department of Chemistry, New York University, made suggestions as to the chemical problems involved.

1. (a) Bancroft, F. W.; Kugelmass, I. N., and Stanley-Brown, M.: Evaluation of Blood Clotting Factors in Surgical Diseases with Special Reference to Thrombosis and Embolism and Certain Bleeding Conditions, *Ann. Surg.* **90**:161, 1929. (b) Bancroft, F. W., and Stanley-Brown, M.: Postoperative Thrombosis, Thrombophlebitis and Embolism, *Surg., Gynec. & Obst.* **54**: 898, 1932. (c) de Takáts, G.: Thrombosis and Embolism, in Christopher, F.: *Textbook of Surgery*, ed. 3, Philadelphia, W. B. Saunders Company, 1941. (d) Wright, H. P.: Adhesiveness of Blood Platelets in Normal Subjects with Varying Concentrations of Anticoagulants, *J. Path. & Bact.* **53**:255, 1941; (e) Changes in Adhesiveness of Blood Platelets Following Parturition and Surgical Operations, *ibid.* **54**:461, 1942. (f) Homans, J.: *Diseases of the Veins*, New England J. Med. **231**:51, 1944.

2. Link, K. P.: The Anticoagulant from Spoiled Sweet Clover Hay, in *Harvey Lectures*, Lancaster, Pa., Science Press, 1944, vol. 39, p. 162.

3. (a) Cahan, A.: Hemorrhage and Purpura Caused by Dicoumarin, *New England J. Med.* **228**: 820, 1943. (b) Evans, J. A.: Dicoumarol Therapy in Thrombotic Emergencies, *ibid.* **230**:131, 1944. (c) Barker, N. W.: The Use of Dicoumarol in Surgery, *Minnesota Med.* **27**:102, 1944. (d) De Bakey, M.: Dicoumarin and Prophylactic Anticoagulants in Intravascular Thrombosis, *Surgery* **13**:456, 1943. (e) Schlevin, E. L., and Lederer, M.: Uncontrollable Hemorrhage After Dicoumarol Therapy with Autopsy Findings, *Ann. Int. Med.* **21**:332, 1944.

4. Brambel, C. E., and Loker, F. F.: Significance of Variations of Prothrombin Activity of Dilute Plasma, *Proc. Soc. Exper. Biol. & Med.* **53**:218, 1943.

5. (a) de Takáts, G.: Heparin Tolerance: A Test of the Clotting Mechanism, *Surg., Gynec. & Obst.* **77**: 31, 1943. (b) Waugh, T. R., and Riddick, D. W.: A Test for Increased Coagulability of the Blood, *Canad. M. A. J.* **50**:547, 1944.

6. Brambel, C. E., and Loker, F. F.: (a) Application of Dicoumarin (3,3'-Methylene-Bis-4-Hydroxycoumarin) in Trauma and Gangrene, *Arch. Surg.* **48**:1 (Jan.) 1944; (b) footnote 4.

sible to correlate decreased response to heparin with the clinical conditions just mentioned. Recently another method^{5b} has been reported, in which varying amounts of heparin are added to drawn blood to ascertain differential clotting rates. The results obtained with the two methods, using this anticoagulant, are comparable. It is especially noteworthy that these methods, employing an entirely different principle, yield information identical with that obtained with the procedure for determining prothrombin clotting time with dilute plasma.

MEASUREMENT OF PROTHROMBIN ACTIVITY

One approach to the solution of the problems of thrombophilia and control of the coagulative processes during administration of dicoumarin is the development of a critical and dependable laboratory technic for evaluating prothrombin activity. This procedure should be of such simplicity that any general hospital would be able to carry it out and obtain reliable and comparable results. Three methods for measuring prothrombin activity have been developed since Howell's noteworthy investigations,⁷ i. e., the Quick,⁸ Warner, Brinkhous and Smith⁹ and Dam and Glavind.¹⁰ Unfortunately, the values obtained with these procedures have not been satisfactorily interpolated, since the methods differ widely in principle.

Warner, Brinkhous and Smith⁹ developed an elaborate two stage technic, which, they stated, takes cognizance of all the factors in the coagulation process. The prothrombin in a sample of defibrinated plasma is first completely converted to thrombin with thromboplastic substance derived from beef lung. Fibrinogen is added to serial dilutions of the resulting thrombin solution until a given dilution yields minimum clotting time. Results are expressed in terms of percentage of prothrombin. The complexity of the technical details involved has restricted its general application.

Dam and Glavind¹⁰ used a standardized tissue extract and estimated prothrombin activity in terms of the amount necessary to induce coagulation in three minutes in a sample which had been treated with heparin method, likewise, has found limited use.

Quick's¹¹ investigations yielded a reliable laboratory procedure for determining prothrombin activity of human plasma. This involves the addition of an excess of thromboplastic substance, obtained from acetone rabbit brain, in the presence of an excess calcium ion concentration. The clotting time, in seconds, is considered to be a measure of the amount of prothrombin present. It has, generally, proved to be the most satisfactory method to date and has the advantage of simplicity of application; also, it can be performed with minimum training and is readily adaptable to numerous determinations. Extensive use of this method has been made to study hemorrhagic diatheses with satisfactory results. It can be more easily adapted to follow prothrombin activity during administration of dicoumarin and to detect clotting tendency of intracorporal blood. An attempt is made here to analyze and to determine the factors involved.

MATERIAL AND METHODS

1. *Thromboplastic Substance*.—Quick's¹¹ method for the preparation of dehydrated rabbit brain thromboplastic substance is followed in detail. The meninges and the blood were removed from fresh rabbit brains and the brains were washed in isotonic solution of sodium chloride. The brain tissue was then transferred to a mortar containing anhydrous acetone and was macerated with a pestle. Fresh acetone was repeatedly added until a fine granular product was obtained. Ten changes of acetone should not require more than fifteen minutes. The resulting product was suspended in fresh acetone and poured over a suction filter. The treated material was washed on the filter with about 400 cc. of acetone and allowed to dry by suction for thirty minutes. The filter was then transferred to a vacuum desiccator, evacuated and allowed to remain eight to ten hours. The dry material then presented a coarse granular appearance. The product was stored in a tightly stoppered bottle in a refrigerator. Such preparation kept its potency for two months in these conditions, without having to be sealed in ampules under vacuum.

(a) Quick's Thromboplastic Reagent: Quick's method of preparation is summarized as used in this investigation. Three hundred milligrams of the coarse granular material, obtained according to the method just described, was suspended in 5 cc. of 0.85 per cent saline solution containing 0.1 cc. of tenth-molar solution of sodium oxalate. After gentle stirring, the mixture was placed in a water bath maintained at 59 C. and then incubated for fifteen minutes. After eight minutes the tube was gently agitated to resuspend the coarse particles. At the end of the incubation period the suspension was centrifuged at a slow speed for about

7. Howell W. H.: The Condition of the Blood in Hemophilia, Thrombosis and Purpura, *Arch. Int. Med.* 13:76 (Jan.) 1914.
8. Quick, A. J.: The Nature of the Bleeding in Jaundice, *J. A. M. A.* 110:1658 (May 14) 1938.
9. Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study on Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions. *Am. J. Physiol.* 114:667, 1936.
10. Dam, H., and Glavind, J.: Determination of Vitamin K by the Curative Blood-Clotting Method, *Biochem. J.* 32:1018, 1938.

11. Quick, A. J.: The Hemorrhagic Diseases and the Physiology of Hemostasis, Springfield, Ill., Charles C Thomas, Publisher, 1942.

ten seconds, when a translucent supernatant free from larger particles resulted. If, however, the dehydrated brain suspension was shaken at intervals during incubation, the resulting preparation frequently did not bring about coagulation of normal undiluted plasma in eleven to twelve seconds. A clotting time of twelve to fourteen seconds was obtained instead. However, when the reagent was properly prepared, Quick's values were consistently obtained during this investigation, namely, eleven to twelve seconds for normal undiluted plasma and thirty-four to thirty-six seconds for normal 12.5 per cent plasma (table 1).

(b) Recommended Thromboplastic Reagent (arbitrarily designated B. F.): A portion of the coarsely granular, acetone-dehydrated rabbit brain was placed in a mortar and ground dry with a pestle into a fine powder. Two hundred and fifty milligrams of this powder was suspended in 5 cc. of 0.85 per cent saline solution containing 0.1 cc. of tenth-molar solution of sodium oxalate. The tube was shaken to insure uniform distribution of the particles and placed in a water bath maintained at 50 C. The suspension was thoroughly shaken at two minute intervals during the total incubation period of fifteen minutes. At the end of this time the suspension was centrifuged twenty seconds to remove the coarser particles. A milky, opaque supernatant was obtained. This emulsion brought about the coagulation of normal undiluted plasma in thirteen to fifteen seconds and of normal 12.5 per cent plasma in eighty-five to ninety-five seconds (table 1). No difficulty was experienced in duplicating the desired clotting time for undiluted normal plasma. On some occasions, however, a clotting time of seventy to eighty seconds for 12.5 per cent plasma resulted. Such an emulsion can be corrected by resuspension of the residue by means of shaking and recentrifuging. This variability has been observed rarely.

2. *Calcium Chloride Solution.*—The concentration recommended by Quick in his earlier paper was 0.025 molar. This molarity was selected and used throughout the present investigation in conjunction with the modified thromboplastic reagent (designated as B. F.) that was developed.

3. *Technic.*—Four and one-half cubic centimeters of freshly drawn blood was introduced into a graduated centrifuge tube containing 0.5 cc. of tenth-molar solution of sodium oxalate. The tube was inverted several times and centrifuged to obtain clear plasma.

In the performance of the test, 0.1 cc. of clear plasma was placed in a small tube, to which 0.1 cc. of modified thromboplastic reagent (B. F.) was added. After thorough shaking of the contents, 0.1 cc. of 0.025 molar solution of calcium chloride was added to the mixture. A stopwatch was started and the tube placed immediately in a water bath adjusted to 37.5 C., in which it was tilted back and forth until the formation of a firm clot was observed. Normal undiluted plasma coagulated in thirteen to fifteen seconds.

Five-tenths cubic centimeter of clear, oxalated plasma was added to 3.5 cc. of 0.85 per cent saline solution to obtain a 12.5 per cent dilution. One-tenth cubic centimeter of this diluted plasma was pipetted into each

of two small tubes. Thromboplastic reagent and calcium chloride solution (0.1 cc. each) were added to each one, and both tubes were placed in the water bath. They were tilted back and forth until a web clot appeared at the rim of the meniscus. Normal 12.5 per cent plasma clotted in eighty-five to ninety-five seconds. Usually, the two tubes showed a web clot simultaneously, but if small variations occurred, the two values were averaged.

FACTORS INVOLVED IN QUICK'S METHOD FOR DETERMINING PROTHROMBIN ACTIVITY

Two factors in Quick's method merit careful consideration: (1) the preparation and the coagulation-activating characteristics of the reagent possessing thromboplastic properties and (2) the selection of an optimum calcium chloride concentration. A review of the evolution of Quick's procedure reveals that changes have been introduced since it was first described.¹² The fact that revisions have been made suggests that the role of these two factors has not been completely explored.

Thromboplastin Reagent.—A survey of the available data reveals that this reagent affects the coagulation reaction to a pronounced degree and that its properties determine the characteristics of the prothrombin activity curve. Chart 1 shows curves having different trends, depending on the method of preparation and the source. Thromboplastic substance is not a chemically defined entity but a complex mixture of variable composition.¹³ The biologic behavior of the material is only partially defined. It becomes necessary to rely on reproducibility of biochemical activity rather than on chemical characterization. The details of the method of preparation of this reagent are primary factors governing its reproducibility and applicability.

Several biologic sources of this substance have been investigated and are classified as follows: (1) rabbit brain: (a) acetone-treated tissue extracts,¹⁴ (b) air-dried tissue extracts¹⁵ and (c) fresh tissue extracts¹⁶; (2) beef and rabbit lung;¹⁷ and (3) snake venom.¹⁵ The choice of

12. Quick, A. J.: On the Various Properties of Thromboplastin (Aqueous Tissue Extracts), *Am. J. Physiol.* **114**:282, 1936; footnote 8.

13. Chargaff, E.: Lipoproteins, in *Advances in Protein Chemistry I*, New York, Academic Press, 1944.

14. Bingham, Meyer and Pohle.^{20a} Brambel and Loker.⁴ Butsch and Stewart.^{20c} Page and Russell.^{20d} Quick (footnotes 8 and 19 b). Stats and Bullowa.^{20f}

15. Barker.^{3c} Davidson and MacDonald.^{20k} Magath.^{20l} Shapiro and others.^{20m} Souter and Kark.²⁰ⁿ

16. Hause and Tocantins.^{20g} Lucia and Aggeler.^{20h} Quick.^{19a} Ziffren and others.²⁰ⁱ

17. Quick.^{19a} Ziffren and others.^{20j}

TABLE 1.—Successive Clotting Times Obtained with the Quick and the Modified Thromboplastic Reagent for Patients with Various Clinical Conditions and for Normal Subjects

	Thromboplastin			Thromboplastin			Thromboplastin			Thromboplastin			Thromboplastin			Clinical Conditions															
	Quick		Uundl. 12.5%	B. F.		Uundl. 12.5%	Quick		Uundl. 12.5%	B. F.		Uundl. 12.5%	Quick		Uundl. 12.5%																
	Plasma Clotting Time, Sec.	Uundl. 12.5%		Plasma Clotting Time, Sec.	Uundl. 12.5%		Plasma Clotting Time, Sec.	Uundl. 12.5%		Plasma Clotting Time, Sec.	Uundl. 12.5%		Plasma Clotting Time, Sec.	Uundl. 12.5%																	
1.....	12	35	14	85	12	27	12	27	14	68	12	25	13	62	11	32	14	85	12	30	15	93	12	20	12	30	12	30	12	30	Postoperative
2.....	12	31	13	90	11	21	12	23	13	63	12	23	13	63	12	20	11	60	12	32	14	76	12	33	12	33	12	33	12	33	Postoperative
3.....	11	29	11	95	13	21	13	21	16	64	14	40	17	105	12	32	14	62	12	30	13	61	12	38	12	38	12	38	12	38	Postoperative
4.....	12	32	13	78	12	21	13	21	16	62	12	28	13	66	12	29	14	62	12	30	14	65	12	39	12	39	12	39	12	39	Postoperative
5.....	12	31	13	65	12	22	12	22	13	47	13	23	13	51	12	24	13	51	11	23	13	52	12	30	12	30	12	30	12	30	Postoperative
6.....	12	30	11	75	12	25	12	25	11	60	12	20	11	65	12	26	13	75	12	30	14	85	12	30	12	30	12	30	12	30	Postoperative
7.....	12	38	11	83	12	24	12	24	13	47	12	27	12	40	11	29	11	61	12	30	14	85	12	35	12	35	12	35	12	35	Postoperative
8.....	12	38	13	95	11	26	12	26	14	60	12	30	13	68	11	32	13	72	12	31	14	80	12	33	12	33	12	33	12	33	Postoperative
9.....	12	35	11	100	12	20	12	20	12	60	11	20	13	50	12	33	13	72	12	31	14	80	12	33	12	33	12	33	12	33	Postoperative
10.....	12	33	13	85	12	25	12	25	13	65	12	28	12	66	12	31	13	73	12	35	11	75	12	35	12	35	12	35	12	35	Postoperative
11.....	12	33	11	69	12	29	12	29	11	60	12	28	11	60	12	32	14	61	12	31	13	64	11	30	12	30	12	30	12	30	Postoperative
12.....	12	36	13	75	12	32	12	32	13	73	12	31	14	69	12	30	15	68	12	31	13	64	11	30	12	30	12	30	12	30	Coronary disease
13.....	12	32	13	60	12	31	12	31	11	61	12	30	13	74	12	31	14	70	12	35	11	68	12	35	12	35	12	35	12	35	Coronary disease
14.....	12	33	13	60	12	31	12	31	11	61	12	30	13	69	11	28	11	63	12	35	11	68	12	35	12	35	12	35	12	35	Coronary disease
15.....	12	30	11	70	12	23	12	23	11	68	12	28	12	67	12	27	14	59	12	31	15	58	12	31	12	31	12	31	12	31	Coronary disease
16.....	12	32	11	60	12	31	12	31	13	61	12	32	12	66	12	30	16	70	12	31	15	58	12	31	12	31	12	31	12	31	Coronary disease
17.....	12	28	13	64	12	28	12	28	13	61	12	30	13	58	12	32	12	65	12	31	15	58	12	31	12	31	12	31	12	31	Thrombophlebitis
18.....	12	29	13	61	12	27	12	27	15	60	11	33	13	62	12	30	13	60	12	31	13	60	12	31	12	31	12	31	12	31	Thrombophlebitis
19.....	12	30	13	58	12	28	12	28	11	62	12	30	13	56	12	31	14	65	12	31	13	61	12	31	12	31	12	31	12	31	Thrombophlebitis
20.....	11	25	13	53	12	28	12	28	11	62	12	29	11	50	12	29	11	60	12	31	13	60	12	31	12	31	12	31	12	31	Thrombophlebitis
21.....	12	26	12	54	12	28	12	28	13	53	12	32	13	56	12	30	13	64	12	31	13	60	12	31	12	31	12	31	12	31	Thrombophlebitis
22.....	12	30	13	54	12	29	12	29	13	54	12	30	13	55	12	30	13	64	12	31	13	60	12	31	12	31	12	31	12	31	Thrombophlebitis
23.....	12	28	12	53	12	28	12	28	11	61	12	29	11	50	12	29	11	60	12	31	13	60	12	31	12	31	12	31	12	31	Thrombophlebitis
24.....	12	31	11	85	12	33	12	33	11	90	12	31	13	91	12	31	13	90	12	31	13	90	12	31	12	31	12	31	12	31	Thrombophlebitis
25.....	12	32	13	100	12	30	12	30	11	97	12	31	13	91	12	31	13	90	12	31	13	90	12	31	12	31	12	31	12	31	Thrombophlebitis
26.....	12	35	13	86	12	38	12	38	13	80	12	32	11	95	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
27.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
28.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
29.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
30.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
31.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
32.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
33.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
34.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
35.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
36.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
37.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
38.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
39.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
40.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
41.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
42.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
43.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
44.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
45.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
46.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12	31	12	31	12	31	Thrombophlebitis
47.....	12	34	14	95	12	35	12	35	14	85	12	35	13	92	12	30	14	98	12	31	14	90	12	31	12						

active substance has, in general, been governed by the minimum clotting time for undiluted normal human plasma. The most widely used source is rabbit brain, and the preparation of greatest activity is acetone-treated rabbit brain tissue. In this connection, special emphasis has been placed on the fact that clotting inhibitors present in brain tissue are removed by treatment with acetone, thereby increasing the activity of the thromboplastic substance.¹¹

The difficulty experienced in the preparation of a reagent from acetone-treated rabbit brain to yield a clotting interval of eleven to twelve seconds for normal undiluted plasma has been mentioned in the section on "Material and

of the thromboplastic substance, resulting in decreased activity; (2) a more concentrated emulsion, obtained as the consequence of agitation, leading to inhibition of the coagulation reaction,¹¹ or (3) the liberation of more clotting inhibitors during such treatment. Apparently, little attention has been paid to small variations in clotting time, amounting to two or three seconds. The differences may have been due to technical errors, such as reading of the stopwatch, variations in the thromboplastic content of rabbit brain or variations in prothrombin activity of plasma from normal persons.

Particles of various sizes were observed in the incubated suspension obtained from acetone-treated rabbit brain which was prepared according to Quick's procedure. In the preceding paragraph, the possibility of liberation of clotting inhibitors as the result of agitation suggested that greater uniformity in activity might be attained if the material was ground dry to a fine powder. A saline suspension of the finely divided thromboplastic substance (prepared as described in the section on "Material and Methods") yielded a milky, opaque suspension, in contrast to the translucent supernatant obtained from the unground, desiccated tissue. This preparation contained finely dispersed particles in suspension, which did not readily settle out on standing. The presence of these particles, however, probably does not affect the properties of the reagent.¹² Analysis showed that this emulsion contained one and a half times as much suspended matter as the emulsion prepared by Quick's method. Also, its biologic activity was readily reproduced, as was evidenced by the fact that several hundred preparations from different lots of rabbit brain consistently gave a clotting interval of thirteen to fifteen seconds for undiluted normal plasma and eighty-five to ninety-five seconds for a 12.5 per cent dilution. For these studies, therefore, Quick's thromboplastic reagent has been modified by grinding dry and thorough shaking during the incubation period.

Calcium Chloride Reagent.—Optimum calcium ion concentration is an important factor in the coagulation of decalcified plasma.¹³ There is no unanimous agreement with regard to the choice of molarity of the solution of calcium chloride used in the routine determinations of prothrom-

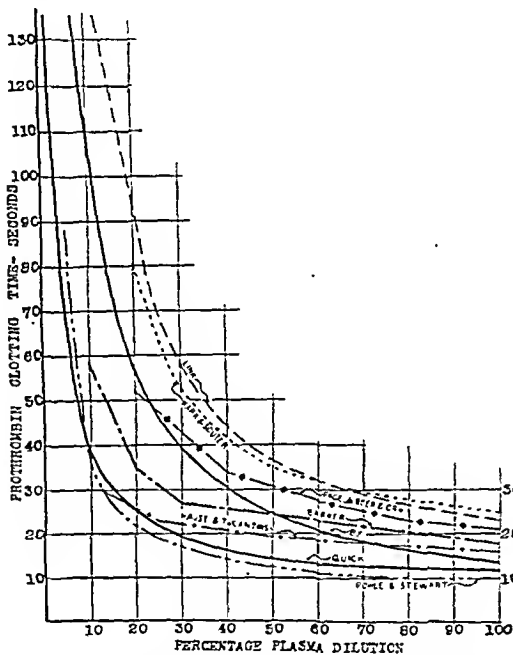


Chart 1.—Comparison of eight prothrombin activity curves of normal human plasma for several types of thromboplastic substance: acetone-treated rabbit brain (Quick,⁸ Pohle and Stewart¹⁹ and B. F. [thromboplastic reagent developed during the course of this investigation]); air-dried rabbit brain (Barker,^{21b} Link and associates²¹ and Souter and Kark²⁰ⁿ); fresh rabbit brain (Hause and Tocantins^{20g}) and snake venom (Page and others^{15b}).

Methods." The observed decrease in activity was found to be directly associated with the amount of shaking during the incubation period. The factors involved may be resolved into the following possibilities: (1) a denaturing process

18. (a) Fullerton.^{20p} (b) Page, R. C.; de Beer, E. J., and Orr, M. L.: Prothrombin Studies Using Russell Viper Venom: III. Effect of Lecithinized Venom on Prothrombin Clotting Time, *J. Lab. & Clin. Med.* **27**: 830, 1942. (c) Page and Russell.^{20d} (d) Shapiro and others.^{20m} (e) Wright and Prandoni.^{20o}

19. (a) Quick, A. J.: The Thromboplastin Reagent for the Determination of Prothrombin, *Science* **92**:113, 1940; (b) Calcium Factor in Quantitative Determination of Prothrombin, *Proc. Soc. Exper. Biol. & Med.* **40**:206, 1939. (c) Pohle, F. J., and Stewart, J. K.: A Study of the Quick Method for the Quantitative Determination of Prothrombin with Suggested Modifications, *Am. J. M. Sc.* **198**:622, 1939.

bin clotting time.²⁰ Lack of uniformity in this factor may be responsible for some of the discrepancies in the values recorded by various investigators. The strength of calcium chloride solution recommended by Quick in his earlier paper was 0.025 molar.⁸ Later, he reported¹¹ a "more suitable" concentration, i. e., 0.020 molar. Other investigators^{10c} have studied the effect of varying calcium ion concentrations on the prothrombin clotting time of undiluted normal plasma. For a given preparation of thromboplastin (Quick) and normal human plasma, Pohle and Stewart^{10c} selected a calcium ion concentration which yielded a minimum clotting time, and they obtained a curve manifesting slightly greater activity than Quick's original curve (chart 1). During the course of the present investigation, 0.025 molar solution of calcium chloride was found to be most satisfactory.

PROTHROMBIN ACTIVITY CURVES

The clot-activating characteristics of the modified thromboplastic reagent developed during the course of this investigation were studied and compared with those of the reagent prepared and described by Quick.¹¹ Prothrombin activity curves were constructed, serial dilutions of normal plasma being used. The diluent employed was 0.85 per cent saline solution. Examination of chart 2 shows that different slopes were obtained for the two preparations. A difference of two or three seconds in the clotting interval was encountered for undiluted plasma, but the deviation became progressively greater on dilution. With 12.5 per cent plasma the difference in the clotting interval for the two preparations was fifty-five seconds. Similar observations were reported in an earlier paper,⁴ but the factors involved in the discrepancy encountered were not understood until the present detailed study was undertaken.

From the data presented, it becomes apparent that preparations of acetone-treated rabbit brain yielding a clotting interval of eleven to fifteen seconds for undiluted plasma do not give any information concerning the characteristics of the prothrombin activity curve unless other points on the curve are experimentally ascertained. Inspection of the two curves (chart 2) further reveals that the slope of the curve obtained with modified thromboplastic reagent is such that small changes in the relative concentration of prothrombin, that is, the variations obtained by dilution of plasma, correspond to appreciable changes in the clotting interval. On the contrary in Quick's curve large changes in concentration of prothrombin correspond to relatively small changes in the clotting time until after a critical point⁸ (hemorrhage level, 20 per cent prothrombin) is attained, when a decided increase in the slope occurs. From this analysis, it is obvious that the modified thromboplastic reagent is more sensitive for detecting variations in prothrombin activity.

The factors responsible for the difference in the characteristics of the slopes of the two prothrombin activity curves (chart 2) may be defined as follows: Dry grinding of the acetone-treated rabbit brain and shaking during the incubation period probably favor the release of clotting inhibitors. Inhibitor substances present in the thromboplastic reagent are of aid in coagulation studies and are not to be considered as undesirable impurities. It seems likely that a satisfactory thromboplastic reagent is one that contains an appropriate balance of prothrombin

20. (a) Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on the Hemorrhagic Agent 3,3'-Methylenbis (4-Hydroxycoumarin): I. Its Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, *Am. J. M. Sc.* 202:563, 1941. (b) Brambel and Loker.⁴ (c) Butsch, W. F., and Stewart, J. D.: Administration of Dicoumarin Compound for Prophylaxis and Postoperative Thrombosis and Embolism: A Preliminary Report, *Arch. Surg.* 45:551 (Oct.) 1942. (d) Page, R. C., and Russell, H. K.: Prothrombin Estimation Using Russell Viper Venom: I. Simple Modification of Quick's Method, *J. Lab. & Clin. Med.* 26:1366, 1941. (e) Quick (footnotes 8 and 19b). (f) Stats, D., and Bullowa, J. G. M.: Effect of a Single Dose of 3,3'-Methylenbis (4-Hydroxycoumarin) upon Blood Coagulation in Humans, *Proc. Soc. Exper. Biol. & Med.* 50:66, 1942. (g) Hause, W. A., and Tocantins, L. M.: Determinations of Plasma Prothrombin Variations in Normal Men and Women, *Am. J. Clin. Path.* 11:54, 1941. (h) Lucia, S. P., and Aggeler, P. M.: The Influence of Liver Damage on the Plasma Prothrombin Concentration and the Response to Vitamin K, *Am. J. M. Sc.* 201:326, 1941. (i) Ziffren, S. E.; Owen, C. A.; Hoffman, G. R., and Smith, H. P.: Control of Vitamin K Therapy: Compensatory Mechanisms of Low Prothrombin Levels, *Proc. Soc. Exper. Biol. & Med.* 40:595, 1939. (j) Barker.²⁰ (k) Davidson, C. S., and MacDonald, H.: A Critical Study of the Action of 3,3'-Methylenbis (4-Hydroxycoumarin) (Dicoumarin), *Am. J. M. Sc.* 205:24, 1943. (l) Magath, T. B.: Technic of Prothrombin Time Determination, *Am. J. Clin. Path. (Tech. Supp.)* 3:187, 1939. (m) Shapiro, S.; Sherwin, B.; Redish, M., and Campbell, H. A.: Prothrombin Estimation: A Procedure and Clinical Interpretations, *Proc. Soc. Exper. Biol. & Med.* 50:85, 1942. (n) Souther, A. W., and Kark, R.: Quick's Prothrombin Test Simplified by the Use of a Stable Thromboplastin, *Am. J. M. Sc.* 200:603, 1940. (o) Wright, I. S., and Prandoni, A.: The Dicoumarin 3,3'-Methylene bis-(4-Hydroxycoumarin): Its Pharmacologic and Therapeutic Action in Man, *J. A. M. A.* 120:1015 (Nov. 28) 1942. (p) Fullerton, H. W.: Estimation of Prothrombin: A Simplified Method, *Lancet* 2:195, 1940.

activators and inhibitors. By varying the inhibitor content, it is possible to alter Quick's prothrombin activity curve to such an extent that a logarithmic plotting yields a straight line, in which the clotting time is closely proportional to the relative concentration of prothrombin.

The effect of clotting inhibitors on the slope of the prothrombin activity curve was tested in the following manner: A thromboplastic substance containing all the inhibitors was selected,

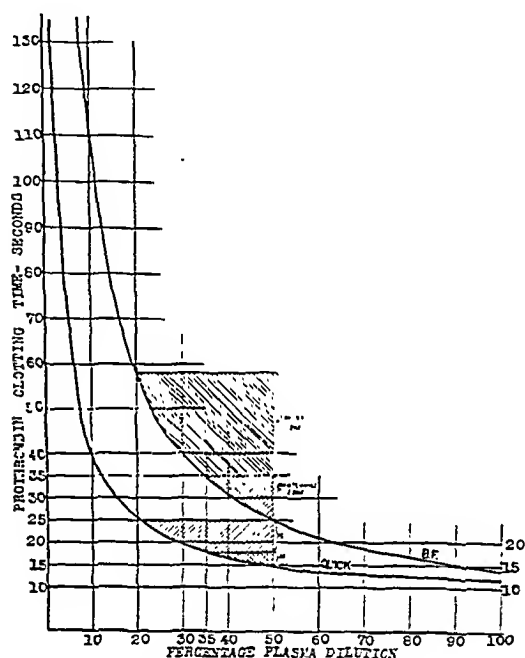


Chart 2.—Comparison of "safety" and "maintenance" zones during administration of dicoumarin for the Quick and the modified (B. F.) thromboplastic reagent. The "safety" zone (hatched area) involves a relative concentration of prothrombin of 35 to 20 per cent (critical hemorrhage level, Quick's) of normal: For B. F. reagent the clotting range is twenty-five seconds, and for the Quick reagent (designated S), seven seconds. The "maintenance" zone (cross-hatched area) involves a relative concentration of prothrombin of 50 to 35 per cent of normal: For B. F. reagent the range of clotting times is ten seconds, and for the Quick reagent (designated M) it is three seconds.

that is, one in which acetone was not used in the process of preparation. The product was prepared by drying it in a vacuum desiccator containing calcium chloride.²¹ A saline suspension of this material was prepared in the same manner as described before (see section "Material and Methods"), and determinations of

prothrombin clotting time were made, using serial dilutions of normal human plasma. A sample of the vacuum-desiccated product was then extracted with large volumes of acetone and again tested in the same manner. The prothrombin activity curves obtained with these two preparations are shown in chart 3. After extraction with acetone a pronounced change in slope and a definite increase in activity were noted. The same chart (chart 3) also shows the effect of reextraction on acetone-treated rabbit brain which has been ground dry, demonstrating a decrease in slope as well as an increase in activity approximating Quick's curve.

Three commercial brands of thromboplastic substance were examined in a similar manner. The prothrombin activity curves obtained revealed that inhibitor substances were reduced to a minimum in them. By virtue of this fact, such preparations possess optimum activity and good reproducibility but decreased sensitivity.

In view of the evidence just presented, it is apparent that two types of thromboplastic substance are now available for studies of the pro-

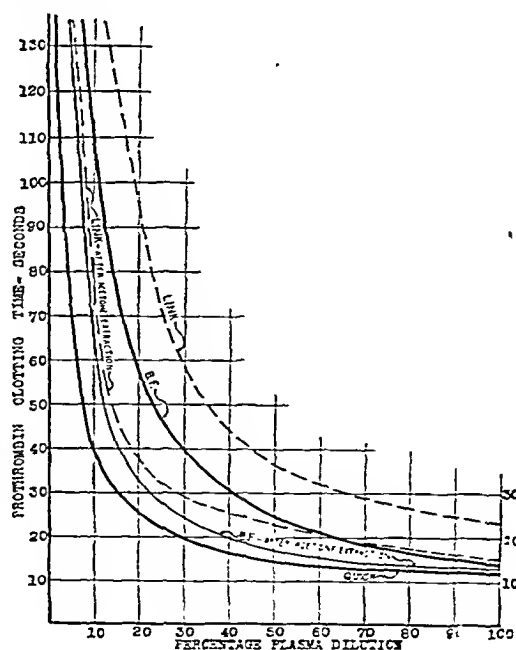


Chart 3.—Effect of extraction with acetone on the activity of thromboplastic substance. The Link²² and the modified (B. F.) preparation are compared. Link's preparation shows the greatest increase in activity after extraction with acetone. The B. F. preparation shows decided increase in activity when the relative concentration of prothrombin is decreased. After extraction with acetone the prothrombin activity curves of the two preparations approach those of Quick's. Normal human plasma was used to construct these curves. This chart shows that acetone removes inhibitor substances from rabbit brain tissue.

21. Campbell, H. A.; Smith, W. K.; Roberts, W. L., and Link, K. P.: Studies on the Hemorrhagic Sweet Clover Disease: II. The Bioassay of Hemorrhagic Concentrates by Following the Prothrombin Level in the Plasma of Rabbit Blood, *J. Biol. Chem.* **138**:1, 1941.

thrombin clotting time by the Quick method. One contains a certain balance of activators and inhibitors, while the other contains a predominance of activators and a minimum of inhibitors. The choice reagent depends on factors determining clinical applicability; that is, the reagent with which the coagulation mechanism is best demonstrated should be employed. Each type can be reproduced as desired.

PROTHROMBIN INHIBITORS AS AGENTS FOR DETECTING A TENDENCY TO INTRA- VASCULAR CLOTTING

It is generally known that in certain clinical conditions increased coagulability of plasma occurs, with resulting intravascular disorders.²² If such enhanced clotting activity is the consequence of an increase in prothrombin activators, an inhibitor present in the thromboplastic reagent should provide a means of detecting them. In tests, the excess activator present would neutralize or counteract the inhibitor, and a lower prothrombin clotting time than normal should result. Such differences in clotting activity in normal and in pathogenic states cannot be demonstrated in undiluted plasma. They are detectable only on dilution, and the selected concentration of plasma is 12.5 per cent with which maximal differences have been obtained. The shortness of the clotting interval, the limitations of experimental error and other factors militate against the use of undiluted plasma. The sensitivity of diluted plasma with respect to variations in prothrombin activity has already been reported in the literature.²³

The validity of the thesis formulated in the preceding paragraph was tested on a series of patients with diverse pathologic conditions involving disorders in blood coagulation (postoperative complications, coronary disease, thrombophlebitis, diabetic gangrene and gangrene resulting from frostbite), as well as on a series of clinically normal persons (table 1). The patients were selected at random and were not treated with dicoumarin during the period of testing. Two types of thromboplastic reagent, Quick's and the modified preparation (B. F.), were used. Undiluted and 12.5 per cent plasma were compared for each person for each test period with both types of thromboplastic reagent. With undiluted plasma no significant variation was observed at any time for any of the different

categories of patients with Quick's reagent or with the modified preparation. Examination of the results obtained with 12.5 per cent plasma reveals great diversities which may form the basis for classification. The data obtained on patients with the aforementioned clinical conditions indicate a decreased clotting interval, which may be interpreted as increased coagulability of plasma. Also, the difference in clotting intervals for dilute plasma and for "normal" plasma was greater when the modified thromboplastic reagent was used, indicating more delicate sensitivity. The subjects in the postoperative group manifested a transient period (six or seven days) of hypercoagulability. Thrombotic complications are likely to occur and have been observed in patients for whom this period has been prolonged, with a clotting interval of forty-five to sixty-five seconds for 12.5 per cent plasma. The patients comprising the other four groups consistently showed a clotting interval of fifty to seventy seconds with the same dilution. The results presented in table 1 demonstrate the clinical applicability of the modified thromboplastic reagent.

The data obtained through the use of inhibitor substances in the thromboplastic reagent capable of detecting a tendency to intravascular clotting correspond with those obtained by de Takáts²⁴ with his technic for testing tolerance to heparin. With both procedures one may apparently evaluate the relative existence of substances that are responsible for hypercoagulability of blood, correlated usually with disturbances of the peripheral vascular system.

STUDIES ON DICOUMARIN

Dicoumarin therapy maintains induced hypoprothrombinemia without hemorrhagic complications. Among the difficulties encountered with use of this type of in vivo anticoagulant, the following phenomena merit special mention: (1) an unusual response after the initial dose, or a "hyperreaction," and (2) an unpredictable response during the course of administration, after an established prothrombin activity level has been maintained in the patient. Technically, the most important problems associated with administration of dicoumarin are as follows: establishment of a margin of safety with respect to hemorrhagic manifestations before they are clinically apparent and interpolation of the results obtained by various procedures and workers. The critical level of prothrombin activity at which bleeding is likely to occur has been defined as 15 to 20 per cent of normal.²⁵ The efficacious therapeutic clotting time level or the decreased percentage of

22. (a) de Takáts.¹⁰ (b) Homans.¹¹

23. Fullerton.^{20p} Campbell and others.²¹ Bramble and Loker.⁶ Sturm, E.: The Prothrombin Concentration in the Plasma of Normal and Leukemic Rats, *Cancer Research* 4:35, 1944. Shapiro and others.^{20m}

24. de Takáts.²⁴

25. de Takáts.²⁵

prothrombin to be maintained during administration of dicoumarin has yet to be generally established. For practical purposes, there should be a "maintenance zone," in which the patient could be kept with little difficulty, and a "safety zone," to take care of unusual responses without the possibility of hemorrhagic complications.

The characteristics of two types of thromboplastic preparation (Quick's and the B. F. reagent) were compared in an effort to ascertain which was more suitable for use after administration of dicoumarin. Fifteen patients who had been treated with varying doses of dicoumarin were selected at random and were studied during five successive testing periods, using both preparations. Forty-eight hours elapsed between each two test periods. The data so obtained are assembled in table 2. Two types of computation of the percentage of prothrombin are also included: namely, an index (ratio of the clotting interval of normal plasma to the clotting interval of plasma treated with dicoumarin) and percentage of prothrombin (the value read from the corresponding activity curve, given the clotting interval).

Inspection of the data presented in table 2 reveals that the values for activity curves for the two thromboplastic preparations studied (chart 2) can be interpolated. If the clotting interval is determined for the modified reagent, the corresponding time can be predicted for Quick's reagent, and vice versa, through a wide range of values. The tabulated figures in some instances deviate slightly from the graphic estimations. The relative percentage of prothrombin obtained as the index is within 8 per cent of the concentration read from the prothrombin activity curve obtained with the modified reagent. However, when the curve obtained with Quick's reagent is used, the percentage difference is greatly increased, demonstrating the unreliability of the index, to be explained later.

Throughout the entire course of clinical investigation of dicoumarin at Mercy Hospital, the choice of a maintenance prothrombin activity level was twenty-five to thirty-five seconds (relative concentration of prothrombin of 35 to 50 per cent) for undiluted plasma. The vast majority (96 per cent) of patients treated showed no signs of hemorrhagic manifestations or thrombotic complications. It was felt that the danger of untoward reactions would be minimized, in view of the degree of sensitivity of the prothrombin activity curve (B. F.). A margin of an additional twenty-five seconds was allowed before the critical level was attained. In chart 2 the activity curves are compared with respect to the choice of a "maintenance zone"

and a "safety zone" for patients treated with dicoumarin. For the same degree of decrease in prothrombin activity the modified preparation gives greater sensitivity than does Quick's preparation. It should be mentioned at this point that some workers treat patients with dicoumarin when the prothrombin concentration is at or near the critical level, i. e., 10 to 30 per cent prothrombin, with satisfactory clinical results, but bleeding in a greater percentage of patients^{2c} (about 8 per cent).

An unpredictable increase in response during the course of administration of dicoumarin is sometimes encountered after the patient has apparently been maintained on an established prothrombin activity level. Such instances, fortunately, have been rare. Some of the factors responsible for the unpredictable response are: increased atmospheric temperature,²⁴ elevation in the patient's temperature and sudden change in the patient's condition. Such circumstances indicate the importance of allowing a wide margin of safety in the selection of a maintenance level of prothrombin activity and of being able to detect sudden changes before the onset of serious consequences.

METHODS OF RECORDING LABORATORY FINDINGS

The interpretation and correlation of the evidence in the current literature on administration of dicoumarin is a difficult task at present because of the lack of uniformity for reporting laboratory findings. Three methods of recording results are in use: (1) prothrombin clotting time of plasma, expressed in seconds²⁵; (2) percentage of prothrombin obtained from the ratio of the clotting time of normal plasma to that of plasma treated with dicoumarin,²⁶ and (3) percentage of prothrombin obtained from normal plasma dilution curves.²⁷ A comparison has been made of two thromboplastic preparations (Quick's and the B. F. reagent) and the data are assembled in table 2. It is my purpose to discuss briefly the relative merits of each one.

24. Richards, R. K.: Influence of Fever upon the Action of 3,3'-Methylene-Bis-(4-Hydroxycoumarin) (Dicoumarol), *Science* **97**:313, 1943.

25. Quick.⁸ Brambel and Loker.^{6a} Page and others (footnotes 20 d and 18 b). Pohle and Stewart.^{19c} Barker.^{2c} Souter and Kark.^{20a} Hause and Tocantins.^{20b} Wright and Prandoni.^{20c} Magath.²⁰¹ Ziffren and others.²⁰¹ Allen, E. V.; Barker, N. W., and Waugh, J. M.: A Preparation from Spoiled Sweet Clover [3,3'-Methylene-Bis-(Hydroxycoumarin)] Which Prolongs Coagulation and Prothrombin Time of the Blood: A Clinical Study, *J. A. M. A.* **120**:1009 (Nov. 28) 1942.

(Footnotes continued on next page)

1. *Prothrombin Clotting Time of Plasma Expressed in Seconds.*²⁵—This form of expression is most generally used. It has the advantage of presenting primary data as obtained in the laboratory without mathematical embellishments. However, different values for normal undiluted plasma have been reported from various institutions, depending on the type of thromboplastic preparation used in the test. The curves presented in chart 1 demonstrate the difficulties encountered. But in the preceding sections the necessity for ascertaining the clotting interval of various dilutions of normal plasma has been stressed as a means of standardization of the thromboplastic reagent. In this manner, undue variations in the values for plasma which has

During the course of the present investigation, two thromboplastic preparations were studied in parallel, with the result that from available prothrombin activity curves and the clotting interval for one preparation, the clotting interval for the other preparation could be obtained graphically (table 2; chart 2). In the same manner, the values for all other types of thromboplastic substances could be interpolated, although such parallel data are not available at present.

2. *Percentage of Prothrombin Obtained from Ratio of the Clotting Time of Normal Plasma to the Clotting Time of Plasma Treated with Dicoumarin.*²⁶—Such an expression is only an index of the clotting time and bears a relationship to prothrombin activity only if the plasma dilution

TABLE 2.—Sensitivity of the Quick and the Modified Thromboplastic Reagent

Thromboplastin								Thromboplastin								Thrombo				
Quick				B. F.				Quick				B. F.				Quick				
Per Cent Pro-thrombin		Plasma Clotting Time, Sec.		Per Cent Pro-thrombin		Plasma Clotting Time, Sec.		Per Cent Pro-thrombin		Plasma Clotting Time, Sec.		Per Cent Pro-thrombin		Plasma Clotting Time, Sec.		Per Cent Pro-thrombin		Plasma Clotting Time, Sec.		
Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %	
1	80	49	15	57	57	51	24	405	80	49	15	58	64	56	22	380	75	44	15	15
2	86	54	14	57	52	59	21	210	86	55	14	54	67	59	21	371	100	100	12	12
3	75	44	16	54	70	63	20	365	71	38	17	74	54	45	29	400	63	31	19	31
4	100	100	12	29	93	90	15	76	100	100	12	84	82	77	17	193	86	55	14	61
5	100	100	12	27	100	100	14	63	51	55	14	46	82	77	17	168	86	55	14	61
6	109	100	11	26	108	100	13	63	52	23	23	55	35	30	40	400	100	100	12	42
7	57	27	21	120	23	28	42	400	80	49	15	50	67	54	21	409	67	34	15	117
8	80	48	15	56	54	48	26	397	71	38	17	82	44	38	32	409	63	31	19	79
9	100	100	12	45	87	55	16	112	80	48	15	56	54	45	26	338	75	44	15	45
10	100	100	12	29	100	100	13	60	92	70	13	45	74	67	19	320	86	54	14	45
11	80	48	15	64	64	57	22	310	75	44	16	71	50	44	23	400	71	35	17	73
12	80	48	15	52	56	50	25	300	86	54	14	56	51	50	25	375	67	34	15	55
13	86	54	14	59	70	63	20	380	65	31	19	79	33	25	42	400	86	54	14	55
14	92	70	13	48	83	79	17	130	80	48	15	62	64	57	22	320	80	53	15	64
15	100	100	11	34	88	85	16	95	86	54	14	55	83	79	17	319	67	34	15	151

been treated with dicoumarin for any given procedure would be minimized. Thus, a therapeutic range in the clotting interval could be established for each modification, e. g., twenty-five to thirty-five seconds, as used at Mercy Hospital (chart 2) or twenty-seven to sixty seconds, as used at the Mayo Clinic. The interpretation of such differences in the range of coagulation time used in dicoumarin therapy becomes perplexing.

26. Evans, J. A.: Problems of Postoperative Thrombophlebitis and Pulmonary Embolism, Connecticut M. J. 8:71, 1944. Wasserman, L. R., and Stats, D.: Clinical Observations on the Effect of 3,3'-Methylenebis (4-Hydroxycoumarin), Am. J. M. Sc. 206:466, 1943. Cahan,^{2a} Zucker, H. D.: Clinical Experiences with Dicoumarol, J. A. M. A. 124:217 (Jan. 22) 1944. Evans, J. A.: Dicoumarol Therapy in Thrombotic Emergencies, New England J. Med. 230:131, 1944.

27. (a) Davidson and Mac Donald.^{20k} (b) Barker, N. W.: Personal communication to the author.

curve is a logarithmic straight line (the logarithm of the clotting time plotted against the logarithm of the relative concentration of prothrombin). The data in table 2 reveal that with the modified preparation a closely approximate proportionality exists but that with Quick's preparation distinct deviations occur. These findings illustrate the applicability of prothrombin inhibitors in the preparation of a suitable activity curve. Attempts at interpolation of the reported findings have been difficult, since this index does not take into consideration such factors as the clot-activating properties of thromboplastic reagent.

3. *Percentage of Prothrombin Obtained from Normal Plasma Dilution Curves.*²⁷—If activity curves are constructed from serial dilutions of normal plasma, the percentage of prothrombin

for plasma which has been treated with dicoumarin can be ascertained with a reasonable degree of accuracy. Standardization and duplication of the clotting interval for dilutions of plasma ranging from 50 per cent downward are essential, because the coagulation rate during treatment with dicoumarin falls in this zone. Inspection of the data in table 2 shows that close agreement of the percentage of prothrombin can be obtained with two thromboplastic preparations if the value is graphically read from the corresponding curve. This evidence indicates that determination of the relative percentage of prothrombin is possible within reasonable limits of experimental error, regardless of the characteristics of the prothrombin activity curves, and

tolerance technic.³² This thromboplastic reagent is easily prepared and reproduced.

The present investigation shows that the presence of inhibitors in the thromboplastic reagent results in an increased sensitivity of the prothrombin activity curve. For use after the administration of dicoumarin, a desirable activity curve is one in which the slope is such that small changes in prothrombin activity can be detected. For detection of such changes Quick's thromboplastic emulsion is not entirely satisfactory. A curve is obtained in which large changes in prothrombin activity correspond to small variations in the clotting interval until a critical level is reached. This point corresponds to prothrombin activity of 15 to 20 per cent. The modified

in Determination of Percentage of Prothrombin and the Plasma Clotting Time

plastin				Thromboplastin								Thromboplastin							
B. F.				Quick				B. F.				Quick				B. F.			
Per Cent Pro-thrombin		Plasma Clotting Time, Sec.		Per Cent Pro-thrombin		Plasma Clotting Time, Sec.		Per Cent Pro-thrombin		Plasma Clotting Time, Sec.		Per Cent Pro-thrombin		Plasma Clotting Time, Sec.		Per Cent Pro-thrombin		Plasma Clotting Time, Sec.	
Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %	Index	Activity Curve	Undiluted	12.5 %
34	48	26	395	67	34	18	80	41	36	24	460	67	24	18	63	28	23	37	400
100	100	14	123	100	100	12	40	67	60	21	168	80	49	15	67	55	51	24	333
40	34	35	400	67	54	18	70	37	28	22	400	80	49	15	60	52	45	27	400
47	41	30	400	71	39	17	68	64	57	22	230	80	49	15	64	51	50	25	230
61	55	23	334	85	54	14	50	48	42	23	400	63	21	12	80	50	43	28	400
74	66	19	282	80	45	15	55	47	41	30	400	71	39	17	70	51	50	25	400
45	40	31	400	60	29	20	120	33	27	43	400	63	31	19	74	44	35	22	400
37	32	38	400	71	38	17	76	41	36	34	400	50	22	24	160	26	21	54	400
47	41	30	400	41	16	29	136	20	16	70	400	43	17	28	112	22	15	62	400
61	54	25	220	92	70	13	32	56	50	25	392	85	54	14	80	61	54	23	390
44	53	32	400	57	26	21	128	32	27	44	400	46	19	26	106	24	20	55	400
39	33	36	400	44	18	27	115	22	18	64	400	33	11	26	152	15	12	24	400
67	50	21	400	71	33	17	69	38	33	37	400	75	44	16	74	48	42	28	400
47	41	30	400	50	22	24	112	27	22	52	400	57	14	32	141	17	14	80	400
37	32	38	400	60	48	15	25	38	33	26	400	80	48	15	80	64	48	26	400

that therefore it is the method of choice for reporting laboratory findings in the literature.

SUMMARY

With a modification of the thromboplastic reagent used in Quick's one stage procedure for determining prothrombin clotting time, coagulation rates deviating from normal can be detected with 12.5 per cent plasma. Undiluted plasma is not satisfactory for this purpose because of the shortness of the clotting interval. Increased clotting rates have been demonstrated by this method for the following clinical conditions: thrombophlebitis, coronary thrombosis, post-operative trauma and gangrene (frostbite and arteriosclerosis). The results so obtained correspond to the findings with de Takáts' heparin

thromboplastic reagent developed during the course of this study possesses the desired properties; that is, for small changes in prothrombin activity a pronounced change in the clotting interval is obtained. The use of such a preparation should greatly minimize the hazards encountered during this type of anticoagulant therapy.

The determination of the percentage of prothrombin from prothrombin activity curves obtained by serial dilution of normal human plasma is recommended. In this manner, uniformity in recording laboratory findings, as well as the definition of a therapeutic prothrombin activity level to be maintained during the course of administration of dicoumarin, could be achieved, which would not be affected by modifications in the procedure.

Calvert and Saratoga Streets.

TRANSPLANTATION OF EPIPHYSIAL CARTILAGE

H. LESLIE WENGER, M.D.

NEW YORK

Many experiments concerned with the transplantation of epiphysial cartilage have been performed in the past, with varying amounts of success. Helferich,¹ Rehn and Wakabayashi,² von Tappeiner,³ Obata⁴ and Heller⁵ all reported some degree of subsequent longitudinal growth of bone. Heller, especially, had remarkably good results in 120 experiments and concluded that autoplasmic reimplantation of the epiphysial plate was successful and that the procedure offered a promise of favorable application in man. Fohl,⁶ working with an epiphysial cartilage plate and a piece of attached diaphysis, likewise expressed the belief that the results justified practical clinical application.

Haas,⁷ on the other hand, has been antagonistic to the procedure on the ground that the epiphysial

cartilage plate loses its power of causing growth of bone after transplantation and that one is not warranted in attempting such a transplantation in a patient with the expectation of obtaining longitudinal growth of bone. Bisgard⁸ similarly decried clinical application of this surgical procedure, because of the "magnitude of the operation and the uncertainty of the results."

The only successful transplantation performed on a human being was that reported by Straub.⁹ In 1912 he transplanted a piece of diaphysis with the epiphysial line and a part of the epiphysis in a child 6½ years of age. A follow-up record made seventeen years later (1929) showed that the epiphysis had survived, grown and continued to function physiologically. Haas challenged this statement and claimed that no longitudinal growth of bone had taken place.

However, the encouraging reports of the earlier workers, the theoretic soundness of the procedure and the tremendous benefits to be derived from a successful operation make even an attempt at transplantation justifiable. Accordingly, in 1941 I transplanted in a child of 7 years the epiphysis of the fibula and part of the attached diaphysis to this first metatarsal bone, which had been almost completely destroyed.

This paper is a report of this unusual operation and the satisfactory results obtained to date. The patient has been observed postoperatively for only four years, and, since he is still growing, the eventual fate of the transplant is, of course, not known. However, the gratifying improvement up to the time of writing and the relative ease of operative technic (it should be within the scope of any well trained orthopedic specialist) have convinced me that it is a valuable procedure and should be attempted on young children when epiphysial centers have been destroyed and growth of bone is desired.

8. Bisgard, J. D.: Transplanted Epiphysial Cartilage, *Arch. Surg.* 39:1028 (Dec.) 1939

9. Straub, G.: Anatomical Survival, Growth and Physiological Function of an Epiphysial Bone Transplant, *Surg., Gynec. & Obst.* 48:657, 1929

Visiting surgeon, New York Post-Graduate Hospital, and instructor in orthopedics, Columbia University College of Physicians and Surgeons.

1. Helferich: Versuche über die Transplantation des Intermediärknorpels wachsender Röhrenknochen, *Deutsche Ztschr. f. Chir.* 51:564, 1899.

2. Rehn, E., and Wakabayashi: Die homoplastische Transplantation des Intermediärknorpels im Tierexperiment, *Arch. f. klin. Chir.* 97:1, 1912.

3. von Tappeiner, F.: Studien zur Frage der Transplantationsfähigkeit des Epiphysenknorpels und des Lakkknorpels, *Ztschr. f. d. ges. exper. Med.* 1:491, 1912.

4. Obata, K.: Ueber Transplantation von Gelenken bei jungen Tieren mit besonderer Berücksichtigung des Verhaltens des Intermediärknorpels, *Beitr. z. path. Anat. u. z. allg. Path.* 49:1, 1914.

5. Heller, E.: Experimentelle Untersuchungen über die Transplantation des Intermediärknorpels in Form der halbseitigen Gelenktransplantation, *Arch. f. klin. Chir.* 104:843, 1914; Versuche über die Transplantation der Knorpelfuge, *ibid.* 109:1, 1917-1918.

6. Fohl, T.: Versuche über die Transplantation der Knorpelfuge, *Arch. f. klin. Chir.* 155:232, 1929.

7. Haas, S. L.: The Experimental Transplantation of the Epiphysis with Observations on the Longitudinal Growth of Bone, *J. A. M. A.* 65:1965 (Dec. 4) 1915; Transplantation of the Articular End of Bone Including the Epiphysal Cartilage Line, *Surg., Gynec. & Obst.* 23:301, 1916; Further Observations on the Transplantation of the Epiphysal Cartilage Plate, *ibid.* 52:958, 1941.

REPORT OF A CASE

D. R., an 11 year old white boy, was injured in 1937 (at the age of 3 years), when some one stepped on his left foot with a hard, sharp high heel. Two days after this accident cellulitis of the foot developed. The condition grew progressively worse, and an operation was performed, which revealed osteomyelitis of the first metatarsal bone. In spite of the use of wet dressings and the usual postoperative treatment, the patient did badly, and because of his desperate condition amputation of the foot was contemplated. It was at this time (1937) that the child came under my care. Physical examination showed that the boy was acutely ill with a temperature of 103 F. Significant findings were limited to the left foot, which was swollen and edematous, with the swelling involving half of the left leg above the ankle. There

approximately four years after the injury, transplantation of the epiphysis of the opposite fibular head was performed, with the following technic.

A 6 inch (15 cm.) incision was made over the lateral aspect of the right knee, and the peroneal nerve was isolated. Adhesive tape was placed around the nerve, and the nerve was followed until all of its terminal branches were found. The head of the fibula and a portion of the shaft, the total section measuring about 2 inches (5 cm.), were resected with an osteotome and a chisel. The wound was then closed, no. 1 plain surgical gut being used for the fascia and muscle and black silk for the skin.

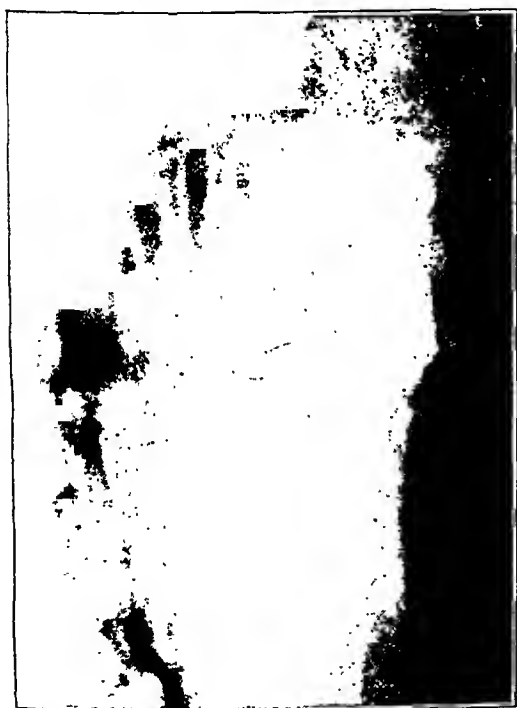


Fig. 1.—Roentgenogram taken shortly after the patient (aged 3 years), was injured, when some one stepped on his left foot, reveals total destruction and dissolution of the first metatarsal bone of the left foot, due to osteomyelitis.

was a draining sinus in the region of the first metatarsal bone.

A roentgenogram (fig. 1), taken on March 22, 1937, showed complete destruction and dissolution of the first metatarsal bone.

The Orr treatment for pyogenic osteomyelitis was immediately instituted, and the patient rallied slowly. The local soft tissue completely healed, and there was some attempt at regeneration of bone. This, however, was incomplete, and the result was extreme shortening of the large toe, with considerable pronation of the foot. Metal arch supports were made to keep the foot in the proper position, but the deformity became worse and operation was indicated. Therefore, on Jan. 28, 1941,

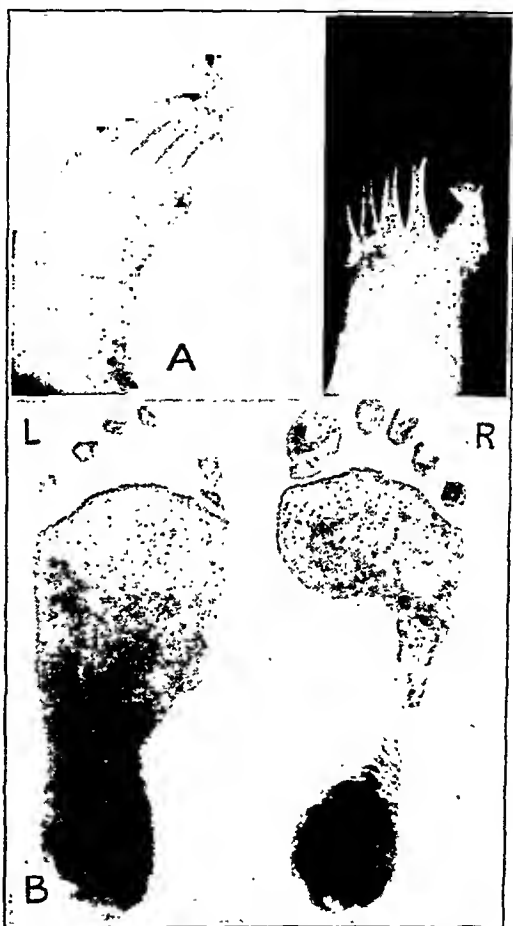


Fig. 2.—A, roentgenogram of the left foot taken before operation shows appreciable regeneration of the first metatarsal bone (fig. 1) but considerable shortening of the shaft and fragmentation of the proximal portion. B, imprint of both feet, made before operation. The toes of the right foot are in normal position. In contrast, the large toe of the left foot is much smaller, and the normal relationship is lost.

A 4 inch (10 cm.) incision was then made on the dorsum of the left foot over the first metatarsal bone, exposing the bone. The shaft of the metatarsal bone was greatly shortened, and the proximal portion was fragmented. This fragmented bone was removed, a small distal section of the healthy bone being left. Forward

traction was then exerted on the great toe, and the epiphysal transplant, including a section of diaphysis from the fibula (which had been trimmed down to 7/8 inch [2 cm.]), was wedged into the space between the distal portion of the metatarsal bone, on one end, and the cuneiform bone, on the other. Throughout the manipulation the bone transplant from the upper end of the fibula was kept scrupulously intact, as far as the epiphysal junction with the metaphysis was concerned. When traction on the great toe was released, the transplant was under sufficient tension to maintain an adequate position, and the toe was appreciably lengthened. The fascia was closed with no. 1 plain surgical gut, and the skin was approximated with silk. A circular plaster cast was applied from the toes to a point above the knee and was left in place for about four weeks.

Recovery was uneventful. When all tenderness of the foot had disappeared, after removal of the cast, the

and he participated in all activities, with no complaint. There was moderate pronation of the foot, which was corrected by an ordinary Whitman arch.

The child recently moved to the Midwest and has been observed by Dr. Frederick C. Kidner, of Detroit, in the past year. A recent roentgenogram (taken on Sept. 2, 1944 and obtained from Dr. Kidner) revealed an increase in length as well as width of the metatarsal bone. The length of this bone is exactly the same as that of the metatarsal in the normal foot. Measurements made shortly after the operation and approximately four years later are given in the table.

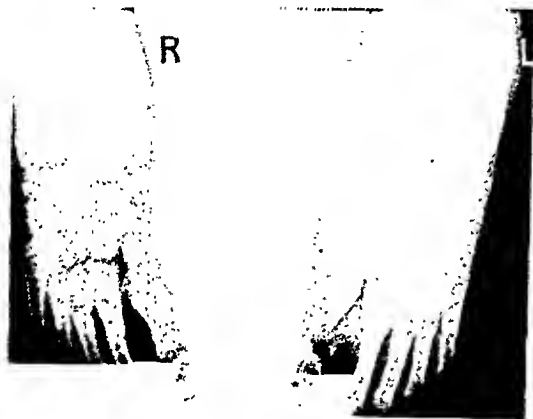


Fig. 3.—Roentgenogram taken approximately two weeks after operation shows that the previously fragmented proximal portion of the first metatarsal bone of the left foot has been removed and that the epiphysal transplant from the opposite fibula, with a small segment of attached diaphysis, is now in situ. The transplant has restored the length of the metatarsal bone, which is now of the same size as that in the normal foot (figs. 1 and 2 A and table).

child was permitted to walk with the aid of an orthopedic shoe and a Whitman metal plate. A roentgenogram (taken Feb. 14, 1941) showed the transplant in situ. This film further showed that the first metatarsal bone of the foot which had been operated on was of the same length as the corresponding bone in the opposite foot. The combined length of the metatarsal and the cuneiform bone was $\frac{3}{8}$ inch (0.3 cm.) shorter on the side of operation.

The child was observed for over two years and was clinically in excellent condition. His gait was normal,



Fig. 4.—A, roentgenogram of the feet taken two years after operation reveals that the first metatarsal bones have grown and are of exactly the same size. B, photograph of both feet taken at the same time as the roentgenogram in A shows a practically normal-appearing large toe on the left foot, which is slightly shorter than the corresponding member on the right foot.

COMMENT

At the time of writing the proximal portion of the epiphysis had lost its anatomic distinctness and appeared to be fused with the cuneiform bone. However, the size of the metatarsal bone which had been operated on had kept pace with the corresponding member on the opposite side.

on this it must be concluded that up to the present the osteogenic properties of the transplant have not been impaired. This is to be expected, since longitudinal growth of bone takes place at the distal end of the epiphysis, at the epiphysal plate and at the proximal end of the epiphysis; fusion of the proximal part of the epiphysis with the cuneiform bone should, therefore, not interfere with growth of the bone.

Why arthrodesis took place in spite of cartilaginous tissue on the epiphysis and the cuneiform bone and a fibrous capsule is interesting, as well

may then be a factor, but it does not appear to be vital at the moment.

Measurements of the First Metatarsal and the Cuneiform Bones

	Left Foot	Right Foot	Comments
Date: Feb. 14, 1941 (approximately two weeks after operation)			
Graft.....	$7\frac{3}{8}$ inch (5 cm.)		
Metatarsal bone	$1\frac{12}{16}$ inches (4.6 cm.)	$1\frac{12}{16}$ inches (4.6 cm.)	Right and left first metatarsal bones of exactly the same size
Metatarsal bone plus cuneiform bone	$2\frac{1}{2}$ inches (6 cm.)	$2\frac{3}{8}$ inches (6.7 cm.)	Normal cuneiform and first metatarsal bones of right foot $\frac{1}{8}$ inch (0.3 cm.) longer than corresponding bones on opposite side
Date: September 1944			
Graft.....	$1\frac{3}{4}$ inches (3.5 cm.)	Graft has grown $\frac{1}{2}$ inch (1.2 cm.) since Feb. 14, 1941
Metatarsal bone	$2\frac{3}{8}$ inches (6 cm.)	$2\frac{3}{8}$ inches (6 cm.)	First metatarsal bones exactly the same size in the two feet
Metatarsal bone plus cuneiform bone	$3\frac{7}{16}$ inches (5.1 cm.)	$3\frac{7}{16}$ inches (5.7 cm.)	Cuneiform and first metatarsal bones of right foot $\frac{1}{4}$ inch (0.64 cm.) longer than corresponding bones on opposite side



Fig. 5.—A roentgenogram taken about four years after operation reveals definite evidence of growth of the first metatarsal bone of the left foot as a result of the transplanted epiphysal cartilage. The measurements of the metatarsal bones in the two feet are identical (table). The proximal portion of the transplant appears to have fused with the cuneiform bone, but longitudinal growth of the metatarsal bone is relatively unimpaired to date.

as important. Generally fusion is dependent on the presence of raw bone surfaces. A tenable explanation may lie in the degree of tension existing between the two bones, the cuneiform and the transplant, after traction on the toe was released. If the entire transplant becomes solidly fused and longitudinal growth of bone is arrested, tension

SUMMARY AND CONCLUSION

Epiphysal cartilage from a fibula, containing a portion of diaphysis, was successfully transplanted to the first metatarsal bone.

The toe, which was greatly shortened prior to operation, was immediately corrected by the transplant.

Observations made over approximately three years show that the transplant has "taken" and is functioning physiologically.

The metatarsal bone in the foot which was operated on is of exactly the same size as the bone in the opposite foot.

The proximal portion of the epiphysis appears to have fused with the cuneiform bone without impairing the growth of bone, which takes place more distally.

The eventual fate of the transplant cannot be prophesied at this time, but the extremely gratifying results obtained to date give assurance that this procedure is valuable.

44 Gramercy Park North.

BLOCKING OF THE MIDDLE CERVICAL AND STELLATE GANGLIONS WITH DESCENDING INFILTRATION ANESTHESIA

TECHNIC, ACCIDENTS AND THERAPEUTIC INDICATIONS
A. DE SOUSA PEREIRA, M.D.
Oporto, Portugal

The progress made recently in the diagnosis and treatment of certain diseases dependent on, or influenced by, stellate ganglion innervation has led to the current practice of blocking this ganglion by the infiltration of procaine hydrochloride.

Although therapeutic indications for this practice are numerous today, the procedure has not been sufficiently popularized among surgeons who are interested in the sympathetic innervation. The principal reason for this lack of popularity is the technical difficulty of blocking the stellate ganglion without accident and in such a way as to be well tolerated by the patient, particularly when repeated blocking with an anesthetic is necessary.

This difficulty has been recognized by all with experience in blocking the stellate ganglion with an anesthetic. The problem results from the deep location of this ganglion and from its close relations to important organs. Owing to the anatomic relations of the ganglion, precise infiltration is difficult (Wertheimer and Trillat¹). Lambret, Razemon and Decoulx² affirmed that infiltration of the stellate ganglion with an anesthetic is a painstaking procedure, whether the anterior, lateral or posterior approach is used.

During the decade since 1934 I have had the opportunity of blocking the stellate ganglion in several hundred cases of the most varied conditions. At first, during the time (1934-1936) in which I worked with Professor Leriche, in Strasbourg, I followed the technic recommended by him and Fontaine.³ Then I tried the technics proposed by Arnulf.⁴ Goinard (cited

by Lambret and associates⁵), Mandl,⁵ White and co-workers⁶ and Wertheimer and Trillat¹ before I decided on the method which I have employed consistently during the last five years; experience with numerous cases has demonstrated that this method is free from hazards, is well tolerated by the patient and is uniformly successful.

I began my investigations by studying the causes of accidents and the difficulties encountered with the technics already known. In all methods of approach to the stellate ganglion until now described, the tip of the needle was always carried close to the ganglion. However, anatomic study of the relations of this ganglion to the vertebral and subclavian arteries and to the pleural cupula showed that these structures may be wounded frequently when the needle is introduced so as to attain direct contact with the stellate ganglion, whether the approach used is anterior or lateral.

This observation led me to search for a point of osseous reference in the deep plane, easy of identification by palpation through the soft tissues, to which the tip of the needle could be directed in order to avoid perforation of the vessels and of the pleural cupula. After a study

4. Arnulf, G.: Infiltration du ganglion stellaire de la chaîne thoracique supérieure par voie supérieure externe, *Presse méd.* **46**:1726, 1938.

5. Mandl, F.: Die Wirkung der paravertebralen Injektion bei Angina pectoris, *Arch. f. klin. Chir.* **135**:495, 1925.

6. (a) White, J. C., and White, P. D.: Angina Pectoris: Treatment with Paravertebral Alcohol Injection, *J. A. M. A.* **90**:1099 (April 7) 1928. (b) White, J. C.; Garrey, W. E., and Aikins, J. A.: Cardiac Innervation: Experimental and Clinical Studies, *Anat. Surg.* **26**:765 (May) 1933. (c) White, J. C.: Diagnostic Blocking of Sympathetic Nerves in the Thorax with Procaine, *J. A. M. A.* **94**:1382 (May 31) 1933. (d) Experimental and Clinical Studies in the Treatment of Angina Pectoris, *Ann. Int. Med.* **7**:113, 1933. (e) Technique of Paravertebral Alcohol Injection: Methods and Safeguards in Its Use in the Treatment of Angina Pectoris, *Surg., Gynec. & Obst.* **71**:1, 1940. (f) White, J. C., and Smithwick, R. H.: Autonomic Nervous System: Anatomy, Physiology and Surgical Application, ed. 2, New York, The Macmillan Company, 1941.

Professor of Surgery, Oporto University Faculty of Medicine.

1. Wertheimer, P., and Trillat, A.: L'infiltration anesthésique de la chaîne thoracique: Technique et résultats, *Presse méd.* **44**:1356, 1936.

2. Lambret, O.; Razemon, P., and Decoulx, P.: Technique de la chirurgie du sympathique et de ses infiltrations, Paris, Gaston Doin & Cie, 1939.

3. Leriche, R., and Fontaine, R.: L'anesthésie isolée du ganglion étoilé: Sa technique, ses indications, ses résultats, *Presse méd.* **42**:849, 1934.

of the topographic relations of the middle sympathetic cervical and the stellate ganglion to the skeleton, the transverse process of the sixth cervical vertebra was taken as the deep point of osseous reference.

Furthermore, study of the morphology and of the normal and pathologic physiology of the cervical and the thoracic portion of the sympathetic trunk convinced me that in order to obtain the most intense vasomotor effect in the upper extremity and in the thorax, it is not enough to anesthetize the stellate ganglion only. It is necessary to anesthetize also the intermediate ganglion, which is located above the stellate ganglion and near the vertebral artery, and the

of the distribution to the organs of the neck, face and cranium. The communicating branches to the fifth and sixth trunks of the brachial plexus arise from the middle cervical ganglion (Gray⁷; Cunningham⁸), and those to the seventh and eighth cervical trunks, from the intermediate and stellate ganglia (Huber⁹; Morris¹⁰). The heart receives, besides the inferior cardiac nerve, which arises from the stellate ganglion, a middle cardiac nerve, originating from the middle cervical ganglion, the largest of the three cardiac nerves (Gray⁷), and a superior cardiac nerve,¹¹ arising from the superior cervical ganglion (Hovelacque¹²). The plexus of the vertebral artery is formed principally from branches arising from the intermediate and the stellate ganglion.

The importance of the middle cervical ganglion in the sympathetic innervation of the upper extremity has already been pointed out by Foerster.¹³ He suggested that the middle cervical ganglion may be a source of postganglionic neurons to the upper extremity and that such fibers would remain intact after stellectomy.

For these reasons, blocking of the anatomic and physiologic group consisting of the middle cervical, the intermediate and the stellate ganglia is essential if one is to obtain a maximum and complete interruption of the vasomotor pathways and the afferent pathways which arise from or cross these ganglia and are distributed in the fields over which the operation is to be done.

Study of the problem of stellate ganglion block resulted in my putting into practice a technical method of blocking the middle cervical and stellate ganglia by an anterior approach. This method has the following advantages: 1. It is devoid of the risk of vascular and pleuropulmonary accidents. 2. It has a deep point of osseous reference, easy to identify by palpation of the transverse process of the sixth cervical

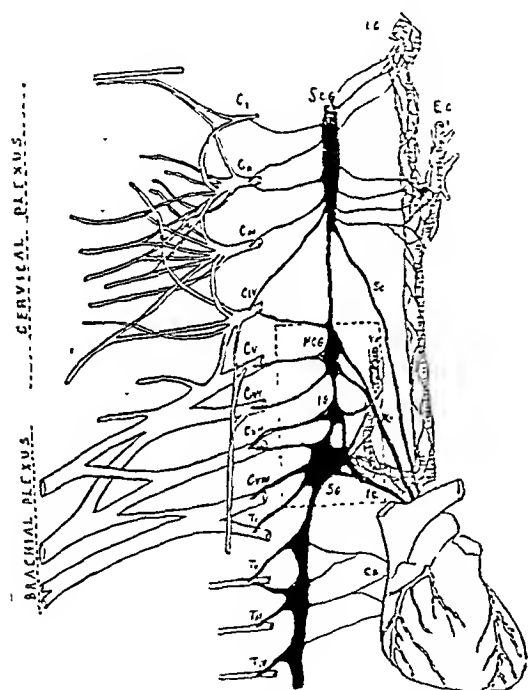


Fig. 1.—The three cervical sympathetic ganglia (middle cervical, intermediate and stellate), from which arise the communicating branches for the brachial plexus, the branches for the vertebral nerve and the two cardiac nerves (middle and inferior). S.C.G. indicates superior cervical ganglion; M.C.G., middle cervical ganglion; I.G., intermediate ganglion; S.G., stellate ganglion; S.C., superior cervical cardiac nerve; M.C., middle cervical cardiac nerve; I.C., inferior cervical cardiac nerve; C.B., sympathetic cardiac branches.

middle cervical sympathetic ganglion, which is normally located at the level of the sixth cervical vertebra.

The middle cervical, intermediate and stellate ganglia constitute an anatomic and physiologic group (fig. 1), which has under its control the vasomotor innervation and the sensory sympathetic pathways of the upper extremity and of the heart, as well as certain portions

7. Gray, H.: *Anatomy of the Human Body*, edited by W. H. Lewis, ed. 23, Philadelphia, Lea & Febiger, 1936.

8. Cunningham, D. J.: *Textbook of Anatomy*, edited by J. C. Brash and E. B. Jamieson, ed. 7, New York, Oxford University Press, 1937.

9. Huber, G. C.: *Piersols' Human Anatomy*, ed. 9, Philadelphia, J. B. Lippincott Company, 1930.

10. Morris, H.: *Morris' Human Anatomy*, edited by J. P. Schaeffer, ed. 10, Philadelphia, The Blakiston Company, 1942.

11. Ranson, S. W.: *The Anatomy of the Nervous System*, Philadelphia, W. B. Saunders Company, 1943.

12. Hovelacque, A.: *Anatomie des nerfs crâniens et rachidiens et du système grand sympathique chez l'homme*, Paris, Gaston Doin & Cie, 1927.

13. Foerster, O.: *Ueber Störung der Thermoregulation bei Erkrankungen des Gehirns und Rückenmarks und bei Eingriffen am Zentralnervensystem*, *Jahrb. f. Psychiat. u. Neurol.* 52:1, 1935.

vertebra. 3. The maximum effect is produced by blocking not only the stellate ganglion but the intermediate and the middle cervical ganglion.

PROPOSED TECHNIQS FOR BLOCKING THE STELLATE GANGLION

The anterior approach was described, in 1934, by Leriche and Fontaine.³ The patient having been placed in dorsal decubitus, with the head raised a little with a pillow and turned to the opposite side, the needle is inserted at the level of the superior border of the clavicle, in the direction of the transverse process of the seventh cervical vertebra. As soon as the tip of the needle is in contact with the bone, a double change of direction is made. By elevation of the hub of the needle, its tip is lowered by an amount corresponding to the height of a vertebra; and, with a rotational movement of 30 degrees, it is carried to the extremity of the horizontal plane. These maneuvers should bring the tip of the needle close to the stellate ganglion.

Practice of this technic showed that it was difficult to obtain anesthesia of the stellate ganglion without the frequent appearance of vascular, neurologic or pleuropulmonary complications. Moreover, the patients complained many times of a deep painful sensation at the time of insertion of the needle, which left an unpleasant impression and caused them to submit unwillingly to repeated blocks of the stellate ganglion.

Lambret, Razemon and Decoulx² admitted that the anterior approach of Leriche and Fontaine³ is an easy and effective method but stated that it is inconvenient in that its points of reference do not offer the desired precision. This disadvantage was also indicated in the investigations of Malherbe (cited by Lambret and associates²), who proposed to infiltrate the stellate ganglion under roentgenoscopic control. Leriche observed also in his patients, especially persons with a short neck, asthma and emphysema, accidents such as perforation of the pleural cupula, the vertebral artery or the brachial plexus. Later Leriche¹⁴ expressed the opinion that the topographic relations of the stellate ganglion in the patient were different from those in the cadaver. Observations made in the course of stellectomy and roentgenographic study revealed that the stellate ganglion, in spite of its contact with the first rib, and by virtue of the forward obliquity of this rib, was purely a cer-

vical organ, even though theoretically it was a thoracic structure. Roentgenographic study of the needle inserted 2 fingerbreadths above the clavicle demonstrated that the tip of the needle touched the transverse process of the seventh cervical vertebra or the neck of the first rib with regularity. Leriche described the technic which he follows. Two fingerbreadths above the clavicle he inserts a needle 8 to 9 cm. long in the direction of the osseous plane, and with a slight downward slant. When the needle is in the right position, it is usually sufficient to inject 10 cc. of 1 per cent solution of procaine hydrochloride, or 20 cc. if one is not certain of the position of the needle.

Goinard (cited by Lambret and co-workers²) practiced an external route of approach, the principal point of reference being the curvature of the first rib, in the supraclavicular fossa. The needle is inserted laterally, immediately above the first rib, into the anterior border of the trapezius muscle and is directed toward the rib with an inclination of 45 degrees. As soon as it reaches the osseous plane, it is advanced in contact with the rib, until it impinges on the body of the vertebra, where the stellate ganglion is located. With the technic of Goinard, identification of the first rib is difficult when excessive accumulation of fat is present in the supraclavicular fossa. Moreover, insertion of the needle in the direction of the intervertebral foramen involves the risk of the anesthetic penetrating into the vertebral canal.

Arnulf⁴ used a superoexternal approach to obtain, with the same insertion, anesthesia of the stellate ganglion and of the first dorsal ganglion. The needle is inserted 5 cm. above the junction of the inner and the middle third of the clavicle, at the level of the posterior border of the sternocleidomastoid muscle. After the fingers have been placed on the supraclavicular fossa, against the prevertebral osseous plane, the needle is inserted obliquely backward and downward, toward the transverse process of the seventh cervical vertebra. The needle is then inclined vertically, and its tip descends in contact with the body of the vertebra. It is not to penetrate from 8 to 9 cm. In this manner it is possible, according to Arnulf, to obtain anesthesia of the stellate and of the first thoracic ganglion. In my first trial with this method the needle penetrated the vertebral artery. Moreover, it is relatively easy for the needle, in its progress downward, to cross the pleural cupula and to penetrate the pleural cavity, or even the lung. Also, the deep points of reference are

14. Leriche, R.: *La chirurgie de la douleur*, ed. 2, Paris, Masson & Cie, 1940.

always easy to palpate at the level of the seventh cervical vertebra. For these reasons I abandoned this technic.

In 1939 Ochsner and DeBakey¹⁵ described a method for stellate ganglion block by the anterior approach which is a modification of the technic of Leriche and Fontaine.³ A needle 80 mm. in length is inserted at a point 1 cm. medial to the midpoint of the clavicle and parallel with its superior border; it is directed horizontally, posteriorly and medially at an angle of 45 degrees with the median sagittal plane. When the point of the needle reaches a depth of 6 to 7 cm., it impinges on the anterolateral surface of the body of the seventh cervical vertebra or on the junction of the seventh cervical and the first thoracic vertebra, where the stellate ganglion lies. Ten cubic centimeters of 1 per cent solution of procaine hydrochloride is injected.

Recently Volpittó and Risteen¹⁶ proposed a new anterolateral approach to the stellate ganglion. Their technic is similar to that of Leriche and Fontaine³ and Ochsner and DeBakey.¹⁵ The seventh cervical transverse process is identified, and a cutaneous wheal is raised 1 cm. above the midpoint of the clavicle. A needle 80 mm. in length is advanced at a 45 degree angle with the sagittal plane of the body downward and medially toward the seventh cervical transverse process. When contact with bone is made, the needle is withdrawn slightly and reinserted downward and inward to insure that the point of the needle is on the first rib. The needle is advanced 1 to 2 cm. until it impinges on bone, and 5 cc. of 1 per cent solution of procaine hydrochloride is slowly injected at this point. The authors stated that they have used this technic successfully in approximately five hundred injections. Owing to the movements which the tip of the needle makes close to the transverse process of the seventh cervical vertebra and to the neck of the first rib, there is a risk that the needle will wound the vertebral artery or the pleura. This approach possesses the advantages and the inconveniences of the technic of Leriche and Fontaine.³

In November 1944 Murphey¹⁷ described a new anterior approach for stellate ganglion block. The patient is placed in a supine position on a firm bed, and the cricoid cartilage and the

scalenus anticus muscle are identified by palpation. A spinal puncture needle is inserted at the lateral edge of the scalenus anticus muscle, at the level of and with the point directed toward the cricoid cartilage. If the needle were inserted with the point directed posteriorly so that the shaft made an angle of from 5 to 15 degrees with the horizontal plane, the needle would pass behind the great vessels and come into contact with the body of the seventh cervical vertebra at a depth of 3, 5 or 6 cm. Ten cubic centimeters of a 2 per cent solution of procaine hydrochloride is then injected. With this approach Murphey observed few complications; there were transitory pain when the deep fascia was pierced and occasional hypesthesia and paresis of the spinal nerves of the corresponding upper extremity, and in 1 case the needle entered the subarachnoid space.

Besides the anterior, the external and the superoexternal approach to the stellate ganglion, there have been reported technics in which this ganglion was reached through the posterior route. Mandl,⁵ in 1925, produced for the first time paravertebral anesthesia of the stellate ganglion through the posterior approach. Later there appeared the technics of White and associates¹⁸ and Wertheimer and Trillat.¹

White¹⁸ places the patient on his side and injects procaine intradermally 4 cm. lateral to the seventh cervical and the upper three thoracic spinous processes. Needles 10 cm. long are then inserted at these points and pushed inward in a direction perpendicular to the skin until the transverse process or the rib is touched; at an average depth of from 2 to 5 cm. It is important (White) to visualize the depth of the ribs in order not to penetrate the pleura and puncture the surface of the lung. Then the tip of the needle is manipulated caudalward until it touches the lower border of the transverse process; the tip of the needle is then 3 cm. from the skin. Each needle is then inclined 20 degrees with the median sagittal plane; when it is thrust inward at this angle, a second contact is made with bone at a further depth of 3 cm. Two cubic centimeters of 2 per cent solution of procaine hydrochloride should be injected through each needle; when signs of paralysis of the sympathetic nerves appear, lasting paralysis is obtained with injection of 5 cc. of 95 per cent alcohol through each needle.

With the technic of Wertheimer and Trillat¹ the point of reference is the first rib, the needle being inserted across the internal part of the first intercostal space. Five or 6 cm. lateral to the

15. Ochsner, A., and DeBakey, M.: Treatment of Thrombophlebitis by Novocaine Block of Sympathetics: Technique of Injection, *Surgery* 4:491, 1939.

16. Volpittó, P. P., and Risteen, W. A.: Stellate Ganglion Block: A Definite Anterolateral Approach, *Anesthesiology* 5:491, 1944.

17. Murphey, D. R.: Stellate Ganglion Block: A New Anterior Approach, *Ann. Surg.* 120:759, 1944.

18. White and White.^{6a} White, Garrey and Atkins.^{6b} White (footnotes 6c, d and e):

spinous process of the first dorsal vertebra, the needle is directed horizontally and inwardly at a certain angle. After having crossed the soft parts, it reaches the transverse process of the first dorsal vertebra. The needle is withdrawn a little and is then oriented in a manner so as to pass above the process, and is pushed forward 2 or 3 cm. New resistance is then encountered, which may be the vertebral body or the head of the first rib. After the needle is withdrawn a little, injection of the anesthetic proceeds.

There exist variations of these technics, such as the methods which were proposed by Paraf and Dreyfus, Le Foyer, and Demarez (cited by Lambret and associates²). The first two authors

no necessity of changes in direction of the needle maneuvers with the needle in the wall of the torso, and periganglionic infiltration of the loose connective tissue of the precostal space. The anterior approach is definitely indicated for patients who cannot be moved because of their condition.

Until 1939 my preference vacillated between the anterior approach of Leriche and Fontaine and the posterior approach (Mandl³; White and White^{6a}), which I used when the morphology of the base of the neck contraindicated employment of the anterior route. It happened, however, that with the anterior approach, not only did vascular, pleural and neural accidents occur from time to time, but infiltration anesthesia

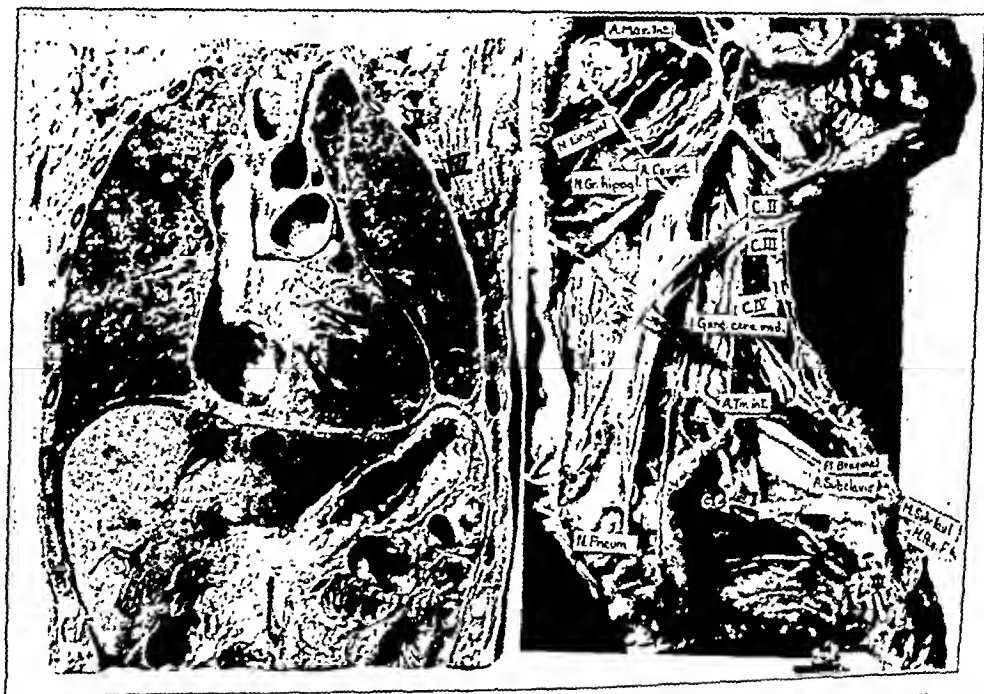


Fig. 2.—Relations of the pulmonary vertex and of the pleura to the first rib (I). The stellate ganglion (100) occupies a deep suprapleural and retropleural location, behind the vertebral and subclavian arteries.

inserted the needle at the level of the seventh cervical spinal process, 4 cm. from the median line. The needle, after having passed around the superior border of the first rib, is advanced about 1 cm., and injection of the anesthetic is begun immediately. With the technic of Demarez the needle is also inserted 4 cm. from the sagittal plane, but at the level of the spinous process of the first dorsal vertebra. Any of these posterior approaches offers less risk and is generally better tolerated than are the anterior approaches.

Lambret, Razemon and Decoux² pointed out various reasons that the posterior approaches are safer: precise osseous points of reference;

was not followed by block of all communicating branches of the brachial plexus, particularly those arising from the middle cervical ganglion.

Also, block of the cervicothoracic sympathetic pathways with any of the technics in which the posterior approach is used (Mandl,³ White and associates¹⁴ and Wertheimer and Trillat¹⁵) is limited to the stellate ganglion and to the superior (second, third and fourth) thoracic sympathetic ganglions. The intermediate ganglion, located above and close to the vertebral artery; the middle cervical ganglion, located on a level with the sixth cervical vertebra, as well as the communicating branches of these two ganglions, and the middle cardiac nerve are not blocked when

he anesthetic is injected dorsally at the level of the first intercostal space or below.

After reviewing the various methods for block of the sympathetic ganglions, I studied carefully the topography and the relations of the middle cervical, intermediate and stellate ganglions to the skeleton, to the vessels and to the pleural cupula and tried to devise a technic by which anesthesia of these ganglions could be obtained with minimum risk to the patient and with maximum probability of success.

MORPHOLOGY AND RELATIONS OF THE MIDDLE CERVICAL AND STELLATE GANGLIONS

The stellate ganglion, which results from fusion of the inferior cervical and the first thoracic sympathetic ganglion, constitutes a physiologic entity characterized by its relations to the cervicodorsal roots through the communicating branches. This ganglion appears in some

muscle, posteriorly by the anterior surface of the transverse process of the seventh cervical vertebra and by the anterior surface of the neck of the first rib and anteriorly by the vertebral artery. The axis of the stellate ganglion is directed obliquely downward and inward, its posterior surface resting above on the transverse process of the seventh cervical vertebra and below on the neck of the first rib. In this position, the stellate ganglion is wrapped in a soft cellular-adipose tissue, which is easily separated when the stellate ganglion is isolated for the purpose of stellectomy.

The relations of the stellate ganglion to the vessels and the nerves must be understood.

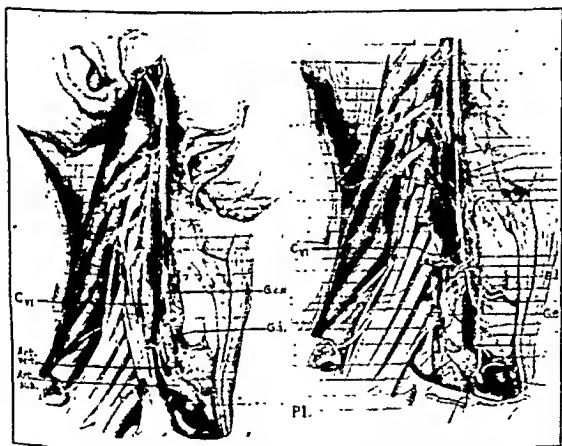


Fig. 3.—Relations of the intermediate (G.i.) and the stellate ganglion (G.c.) to the vertebral artery, to the pleural cupula (P.L.) and to the transverse process of the sixth cervical vertebra. (CIT) (from Hovelacque¹²).

cases to be morphologically divided into two masses, the superoexternal (intermediate ganglion) and the posteroinferior (stellate ganglion). In a large number of cases it is oval and is elongated in a vertical direction, measuring from 1 to 2 cm. in length and 1 cm. in width. Located deep in the superior retropleural fossa (fig. 2), in relation to the vertebral artery and to the first rib, its situation is partly thoracic and partly cervical.

The stellate ganglion is located (fig. 3) in a concavity, which, according to Hovelacque, is limited inferiorly by the posterior aspect of the pleural cupula, medially by the portion of the vertebral column covered with the longus colli muscle of the neck, laterally by the scalenus

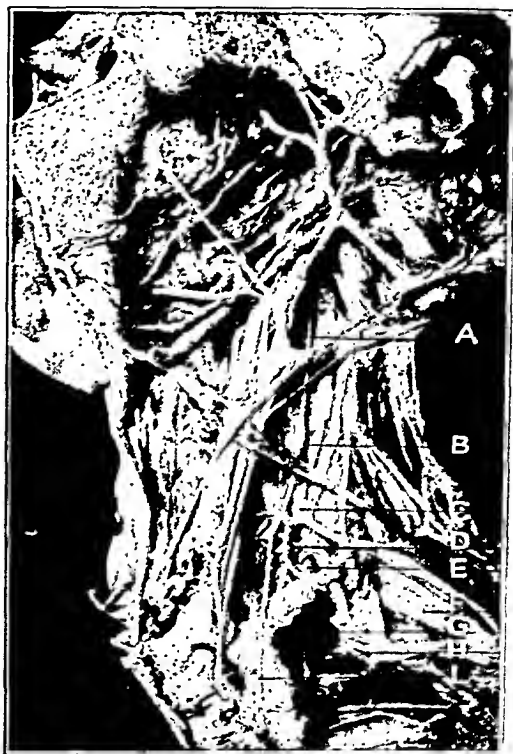


Fig. 4.—Dissection of the cervicothoracic sympathetic system, showing its intimate relations to the vertebral and subclavian arteries. A, cervical sympathetic trunk; B, middle cervical ganglion; C, sixth transverse process; D, intermediate sympathetic ganglion; E, vertebral artery; F, brachial plexus; G, stellate ganglion; H, first rib; I, middle cervical cardiac nerve.

Posteriorly it is in relation with the anterior branch of the eighth cervical nerve, and inferiorly, with the anterior branch of the first dorsal nerve. Its external border is crossed laterally by the intercostocervical arterial trunk, with which it sometimes is in contact. Anteriorly the stellate ganglion is related to the first segment of the vertebral artery (fig. 4). This relation varies according to whether the stellate

ganglion is composed of one mass only or of two masses, one being the intermediate ganglion. When the second ganglion is present, it is located above and medial to the principal mass and alongside and medial to the artery, both ganglions being united by nerve cords which surround the vertebral artery (fig. 5).

The middle cervical ganglion is located in front of the transverse process of the sixth cervical vertebra (fig. 3). From this ganglion arise the communicating branches for the fifth and sixth

envelops the viscera and the vessels before it joins the prevertebral aponeurosis. This disposition of the fascia exists only up to the level of the inferior thyroid artery; below that level the aponeurotic relations are changed, and it is difficult to speak of any closure thereafter. The cellular tissue is loose in front of the prevertebral aponeurosis in the whole inferior region of the neck (fig. 6). This anatomic disposition explains the reason that the anesthetic solution injected in front of the prevertebral aponeurosis, at the level of the sixth cervical transverse process, blocks the middle cervical ganglion and then descends into the prevertebral soft cellular tissue, to reach the stellate ganglion; through further diffusion in the soft cellular tissue surrounding this ganglion, the anesthetic causes block of the ganglion by periganglionic infiltration.



Fig. 5.—Section of the base of the neck made at the level of the seventh cervical vertebra (*C VII*). Notice the relations of the intermediate ganglion with the vertebral artery.

trunks of the brachial plexus and the middle cardiac nerve, the most developed of the three cardiac sympathetic nerves.

Besides the topographic relations of the stellate and middle cervical ganglions, it is also important to know the arrangement of the aponeurosis at the base of the neck, in order to understand the path of diffusion of the anesthetic solution injected, from the level of the transverse process of the sixth cervical vertebra to the position of the middle cervical and the stellate ganglion.

According to Hovelacque,¹² there exist a prevertebral aponeurosis, which covers the prevertebral muscles, and a deep aponeurosis, which



Fig. 6.—The space with soft cellular tissue located in the base of the neck (5), between the prevertebral aponeurosis and the posterior surface of the sheath which encloses the common carotid artery (4), the internal jugular vein (2) and the vagus nerve (1). In a posterior plane is the brachial plexus (3).

PRINCIPLES OF THE TECHNIC OF BLOCKING THE MIDDLE CERVICAL AND STELLATE GANGLIONS BY DESCENDING INFILTRATION ANESTHESIA

A study of the morphology, topography and relations of the stellate ganglion to the vessels and to the pleural cupula and experience acquired

with practice of the methods of infiltration previously explained led me to the conclusion that it was difficult to obtain anesthesia of the stellate ganglion, through the direct approach to this ganglion, without frequently causing a vascular or a pleural accident. Such a conclusion prompted the effort to block the stellate ganglion indirectly, by guiding the needle toward a fixed site easy of identification: it was believed that after the anesthetic solution was injected, it would diffuse downward from this site to anesthetize the middle cervical, intermediate and stellate ganglions.

Such a result was obtained by inserting the needle at the level of the base of the transverse process of the sixth cervical vertebra (fig. 7). In this manner the middle cervical ganglion is blocked and perforation of the vertebral artery is

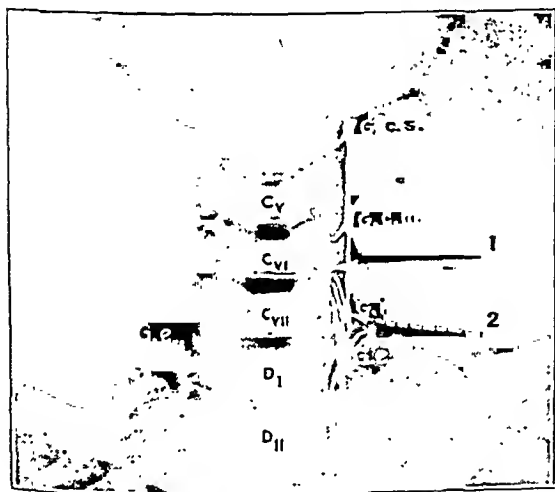


Fig. 7.—Relations of the cervical sympathetic ganglions (middle cervical ganglion, *G.c.m.*: intermediate ganglion, *G.i.* and stellate ganglion, *G.c.*) to the skeleton. (1) approach to the anterior surface of the sixth transverse process; (2) approach to the anterior surface of the seventh transverse process.

avoided. The anesthetic solution, being injected at the apex of the fossa of the stellate ganglion, descends by gravity and infiltrates the soft cellular tissue of the fossa. The stellate and intermediate ganglions and the respective communicating branches are saturated with the anesthetic solution; thus is obtained, simply and without accident, anesthetic block of the middle cervical, intermediate and stellate ganglions (fig. 8). As the communicating branches of the fifth and sixth cervical nerves cross and enter into close relation with the prevertebral muscle mass, this muscle mass is also anesthetized by infiltrating it with 5 cc. of anesthetic solution, which is injected anterior to the transverse process of the

sixth cervical vertebra. This solution, injected into the muscular plane behind the prevertebral aponeurosis, also anesthetizes the sympathetic chain, which at this point lies anterior to the prevertebral aponeurosis. In front of this aponeurosis 15 cc. of the anesthetic solution is injected. The middle cervical ganglion is anesthetized, and the anesthetic solution diffuses in the soft cellular tissue of the fossa of the stellate ganglion and anesthetizes the ganglionic mass, together with the communicating branches to the seventh and eighth cervical nerves and the first dorsal nerve and the deep communicating branches which constitute the vertebral nerve.

In order to promote diffusion of the anesthetic solution, the injection is made with the patient



Fig. 8.—Descending infiltration anesthesia, made at the level of the sixth cervical transverse process, produces block of the middle cervical, intermediate and stellate ganglions. (1) middle cervical ganglion; (2) intermediate ganglion; (3) stellate ganglion; (4) second thoracic sympathetic ganglion.

seated or with the head and neck in an elevated position; this position brings the force of gravity into operation.

The point of osseous reference chosen is the base of the transverse process of the sixth cervical vertebra, and not the clavicle, since roentgenographic studies led to the conclusion that the position of the middle cervical and stellate ganglions in relation to the transverse process of the sixth cervical vertebra is less variable than its position in relation to the clavicle.

TECHNIC OF BLOCKING THE MIDDLE CERVICAL AND STELLATE GANGLIONS BY DESCENDING INFILTRATION ANESTHESIA

The patient is seated facing forward, with his arms at his side. If the patient is not able to sit down, he is placed in dorsal decubitus, with the torso and head raised about 45 degrees; if he cannot look forward, his head is rotated to the side opposite the operator. The transverse process of the sixth cervical vertebra is palpated; this procedure presents difficulty only in patients with a short, fat neck.

After the skin is sterilized, a needle 6 to 8 cm. long, of small caliber, is inserted. The operator stands in front of the patient if the latter is sitting in an elevated position (table or bed), or rests on one knee if the patient is seated on a chair;

ing the deep point of reference against which it is necessary to direct the tip of the needle. The needle is inserted in the anteroposterior direction almost perpendicularly toward the anterior face of the transverse process of the sixth cervical vertebra and directed toward the base of the process, where the sympathetic chain crosses. If the needle is directed toward the tip of the transverse process, diffusion of the anesthetic solution will cause anesthesia of the brachial plexus.

In order to make certain that the needle is in a correct position, it is necessary to feel its point in contact with the bone. As soon as the correct position is obtained, pressure on the hub of the needle is continued, in order to maintain it in contact with the process, and with the



Fig. 9.—Technic of middle cervical and stellate ganglion block with descending infiltration anesthesia.

he requests the patient not to contract the muscles of the neck or to move his head in the course of palpation or during insertion of the needle (fig. 9).

With the tip of the left index finger pointing in an anteroposterior direction, the anterior surface of the transverse process of the sixth cervical vertebra is palpated behind the posterior border of the sternocleidomastoid muscle. With this maneuver, one tries to displace the sternocleidomastoid muscle, the larynx and trachea and the neurovascular bundle of the neck as much as possible toward the midline and over the prevertebral plane. With this displacement, the skin is strongly depressed over the anterior surface of the transverse process of the sixth cervical vertebra, and the end of the index finger is fixed against the osseous plane, thus furnish-

ing a point of reference against which the hand the depressed skin is slid along the neck so that the latter will remain in contact with the bone when the pressure is released. As the left hand releases its hold on the sternocleidomastoid muscle and the neurovascular bundle, the needle, which had been inserted in an anteroposterior direction, is displaced by the recoil of these structures to the horizontal position; as a result, it lies in a somewhat lateral position, times a transverse, position.

After preliminary aspiration to exclude blood, 5 cc. of 1 per cent solution of procaine hydrochloride is injected against the anterior surface of the base of the transverse process; the anesthetic diffuses between the process and the prevertebral aponeurosis and descends to reach the external layer of the vertebral artery and the branch of the vertebral nerve. The tip of the needle

then slowly withdrawn for about 2 or 3 mm., until it is felt to be out of the resistant prevertebral aponeurosis and to be free in the soft cellular tissue which lies in front of this aponeurosis. After a second aspiration to exclude bleeding, 15 to 20 cc. of 1 per cent procaine hydrochloride solution is injected at this point. The anesthetic blocks the middle cervical ganglion, and the solution, descending in front of the prevertebral aponeurosis, in which is located the cervical sympathetic chain, diffuses in the soft cellular tissue which surrounds the vertebral artery and the intermediate and the stellate ganglion. Normally, the middle cervical ganglion; the interganglionic trunk which unites the stellate ganglion and the middle cervical ganglion; the intermediate ganglion, when it is present; the stellate ganglion and all its communicating branches, including the vertebral nerve, are all blocked by the anesthetic solution, which diffuses downward in this plane under the force of gravity.

If during the fifteen minutes which follows injection of the anesthetic there do not appear signs of vasomotor and pain block of the sympathetic innervation of the upper extremity and thorax, however evident are the signs of cephalic sympathetic block, it is apparent that the anesthetic did not diffuse sufficiently (the needle was not placed in the right position, or pathologic conditions of the tissues existed) to block completely the stellate ganglion. In this case, if the inferior cervical sympathetic block is made to interrupt the sympathetic innervation of the upper extremity or of the thoracic organs, the first injection of the anesthetic, made at the level of the sixth transverse process, must be followed by a second insertion, with the needle directed toward the base of the transverse process of the seventh cervical process. The transverse process of the sixth cervical vertebra is identified, and the structures are retracted, as in the technic previously described. An insertion is made about 1.5 to 2 cm. below the transverse process of the sixth cervical vertebra, and the needle is directed toward the base of the transverse process of the seventh cervical vertebra. When the puncture is made at this point, the needle must penetrate deeper than when it is inserted at the level of the sixth cervical vertebra. All the other details of the technic are similar to those which have already been described for insertion at the level of the sixth cervical transverse process. Five cubic centimeters of 1 per cent procaine hydrochloride solution is injected against the osseous plane, and 10 cc. more of the same drug is injected 2 or 3 mm. in front of this plane, into the soft connective tissue. In

this case the tip of the needle normally is close to the intermediate ganglion and the vertebral artery. For this reason the greatest care must be taken not to inject the anesthetic into the vertebral artery. In this way it is possible to obtain safe block of the middle cervical, the intermediate and the stellate ganglion.

Several drugs with a more prolonged action have been proposed as substitutes for procaine in blocking sympathetic ganglions. Novest-Oil¹⁹ was used by Brenner²⁰ for prolonged analgesia in a group of cases of rectal disorders, and it was also employed by Belinkoff²¹ for intercostal block in operations on the upper part of the abdomen. Recently Lee²² employed monobromosalicyl alcohol for the purpose of obtaining prolonged anesthesia of the stellate and lumbar sympathetic ganglions. The value of this drug, according to Lee, is in its reducing the number of injections required in cases in which repeated sympathetic block is indicated.

In cases in which blocking of the stellate ganglion must be done at short intervals I have employed a solution of 1 per cent procaine hydrochloride. Such blocks were always well tolerated by the patient, were followed by satisfactory results and did not produce neuritis. In cases in which stellectomy was done, after repeated blocks, no difficulty either in the approach to or in the isolation of the stellate ganglion was encountered. The only abnormality noted was that the operative wound bled more than usual, owing to vasodilatation.

CLINICAL SIGNS INDICATIVE OF SUCCESS OF BLOCK OF THE MIDDLE CERVICAL AND STELLATE GANGLIONS

A few minutes after injection of the anesthetic solution, the patient begins to show signs of the Bernard-Horner syndrome (fig. 9). There are miosis of the pupil, ptosis of the upper lid and slight elevation of the lower lid, with narrowing of the palpebral fissure, and enophthalmos. The conjunctiva becomes congested, owing to vasodilatation of its vessels. These signs become progressively accentuated for fifteen or twenty

19. Novest-Oil is a solution of monoisobutylaminoethylparaaminobenzoate hydrochloride base, benzyl alcohol and ethyl aminobenzoate in expressed oil of almond.

20. Brenner, J. M.: Novest-Oil: A New Prolonged Oil Analgesic, *J. Nat. Proct. A.* **14**:244, 1942.

21. Belinkoff, S.: Intercostal Block with Long-Acting Anesthetic in Upper Abdominal Operations, *Anesthesiology* **5**:500, 1944.

22. Lee, C. F.: *Am. J. M. Sc.*, 1945, to be published.
Lee, C. F.; Macht, D. L. and Pierpont, R. Z.: A Preliminary Report on a Method for Lengthening the Effect of a Sympathetic Nerve Block, *Bull. Johns Hopkins Hosp.* **74**: 119, 1944.

minutes, when they present their maximum intensity. About one hour later they begin to diminish and to disappear.

The face and the ear on the side of block of the stellate ganglion often become red, and the patient feels a burning sensation. Anhidrosis is observed on the same side of the head and the corresponding upper extremity. In the upper extremity, especially the hand, the patient feels a burning sensation. The hand and the forearm become warm, signs of vasodilatation being seen at the level of the fingers.

The oscillometric index for the arm and forearm is increased after block of the middle cervical and stellate ganglions.

ACCIDENTS WHICH MAY OCCUR IN THE COURSE OF BLOCKING THE MIDDLE CERVICAL AND STELLATE GANGLIONS

It was the frequency of pleuropulmonary and vascular accidents, such as perforation of the subclavian or vertebral arteries, which led me to abandon the technic of stellate ganglion block by direct injection into this ganglion.

With the technic which I have employed for five years, in hundreds of cases, no pleuropulmonary accident has been observed. Only occasionally has the inferior thyroid or the vertebral artery been punctured; this accident was especially likely to occur when the tip of the needle was directed toward the base of the transverse process of the seventh cervical vertebra. Besides always employing a fine needle, I make it a rule to aspirate before injecting the anesthetic solution, in order to avoid intra-arterial injection.

I have never entered the intervertebral foramen, since I am careful to insert the needle in an anteroposterior direction and to keep the tip in contact with the anterior surface of the transverse process during the external rotation which it undergoes when the sternocleidomastoid muscle returns to its resting position.

It is possible for the needle to perforate the trunk of one of the cervical nerves if, instead of passing in the direction of the transverse processes of the sixth and seventh cervical vertebrae, it penetrates the space between the transverse processes of these vertebrae. In order to avoid this accident, the tip of the needle is directed toward the base of the transverse process.

I have never observed any complications other than a slight vertiginous condition in a few patients, which did not necessitate special care and which disappeared completely within one hour after the block.

THERAPEUTIC INDICATIONS FOR BLOCK OF THE MIDDLE CERVICAL AND STELLATE GANGLIONS WITH AN ANESTHETIC

Since the investigations initiated in 1925 by Leriche and Fontaine²³ on the clinical indications for and the technic of block of the stellate ganglion, the field in which this therapeutic measure has shown its valuable results has expanded considerably.

Therapeutic indications for block of the middle cervical and the stellate ganglion are deduced from knowledge²³ of the influence which physiologic interruption of these ganglions exerts on the organs which they innervate. Blocking of these ganglions produces a vasomotor effect which is evident in the corresponding half of the head, face and neck; it extends to the heart and to the respiratory apparatus and from the larynx to the bronchial extremities (Leriche²⁴), and it is intense in the arm on the same side. This vasomotor effect is of much longer duration than that produced by simple anesthesia. The vasomotor change consequent on blocking of the middle cervical and stellate ganglions is of the nature of vasodilatation, with increase in the local temperature, the oscillometric index and the peripheral circulation.²⁴ These effects constitute important indications for its use in the relief of vasoconstriction in any zone innervated by these ganglions or in the activation of the circulation when it is locally decreased.²⁵

Thus, in cases of cerebral vasospasm, the indication for block of the middle cervical and stellate ganglions is based on the physiologic interruption of cerebral vasomotor pathways. Investigations of several authors (Orr and Sturrock,²⁶

23. Braeucker, W.: *Der Brustteil des vegetativen Nervensystems und seine klinisch-chirurgische Bedeutung*, Beitr. z. Klin. d. Tuberk. 66:1, 1927. Gask, G. E.: *The Surgery of the Sympathetic Nervous System*, Brit. J. Surg. 21:113, 1933. Kuntz, A.: *Autonomic Nervous System*, Philadelphia, Lea & Febiger, 1934.

24. de Sousa Pereira, A.: *L'infiltration novocainique du ganglion étoilé: Bases expérimentales et applications cliniques*, Arch. d. mal. du cœur, 1941, p. 1.

25. Bird, C. E.: *Sympathectomy as Preliminary to Obliteration of Popliteal Aneurism*, Surg., Gynec. & Obst. 60:926, 1935. Gage, M.: *Mycotic Aneurism of the Common Iliac Artery: Sympathetic Ganglion Block as an Aid in the Development of the Collateral Circulation in Arterial Aneurism of the Peripheral Arteries*, Am. J. Surg. 24:667, 1934. Lehman, E. P.; Rawles, B. W., and Murphey, D. R.: *Sympathectomy in Acute Arterial Occlusion: An Experimental Study*, South. M. J. 26:246, 1933. Theis, F. V.: *Effect of Sympathetic Neurotomy on the Collateral Arterial Circulation of the Extremities: Experimental Study*, Surg., Gynec. & Obst. 57:737, 1933.

26. Orr, D., and Sturrock, A. C.: *Toxi-Infective Lesions in the Central Nervous System: The Influence of Disturbance of the Sympathetic Mechanism on Their Localization*, Lancet 2:267, 1922.

Forbes and associates,²⁷ Talbot and co-workers,²⁸ Cobb,²⁹ Chorobski and Penfield³⁰) have shown that innervation of the cerebral vessels is similar to that of the arterial systems in other regions and organs. Interruption, by block of the middle cervical and stellate ganglions, of the sympathetic innervation of cerebral vessels produces vasodilation of the cerebral vessels on the same side of the brain. Volpitto and Risteen,³¹ by direct inspection of the cortex of 2 patients immediately after block of the stellate ganglion, noted an increase in the caliber of the pial vessels. These authors observed that patients with a condition diagnosed as cerebral thrombosis showed improvement immediately or several hours after block of the stellate ganglion with procaine. This improvement varied from partial to complete recovery. Also, a patient with frequent attacks of cerebral vasospasm showed great improvement immediately after block of the stellate ganglion. In cases of thrombosis of the posterior inferior cerebellar artery, the reflex spasm is abolished and dilation of collaterals is produced by block of the stellate ganglion with procaine (Hickcox, Tovell, Raskind and Scoville³²).

In cases of circulatory disturbances³³ of the upper extremity in which there is ischemia³⁴ and in cases of arterial embolism,³⁵ thrombophle-

bitis,³⁶ atonic ulceration, post-traumatic edema³⁷ and post-traumatic osteoporosis, good results have been obtained with repeated blocks of the middle cervical and stellate ganglions with procaine. In the reflex arteriospasm which accompanies the embolic phenomenon, the pain may be relieved and the collateral circulation increased by interruption of the vasoconstrictor fibers through blocking the middle cervical and stellate ganglions with procaine. According to Hickcox and co-workers,³² the arteriospasm in Raynaud's disease or an acute arteriospasm, traumatic in origin or associated with the embolic phenomenon may be relieved by stellate ganglion block.

Asthmatic crises have been relieved by means of stellate ganglion block, possibly through vasomotor control, which produces changes in the bronchial and tracheal mucosa, and through action on the bronchial muscles (Leriche). A favorable therapeutic result was obtained by Fontaine in cases of acute edema of the lung. The effect of this procedure has also been studied in cases of experimentally induced pulmonary embolism.

Concerning the influence of stellate ganglion block on coronary³⁸ and heart disease,³⁹ Leriche¹⁴ stated that in cases of angina pectoris and tachycardia the painful phenomena disappear and the rhythm of the heart is regularized. In the treatment of cardiac pain in angina pectoris, White and associates⁶ stated they preferred alcoholization of the stellate ganglion and of the second, third and fourth thoracic ganglions to repeated blocks with procaine. With the paravertebral block of Mandl⁵ or with the alcoholization of the stellate and upper thoracic ganglions (Swetlow,⁴⁰ White and co-workers,¹¹

27. Forbes, H. S., and Wolff, H. G.: The Cerebral Circulation: III. The Vasomotor Control of the Cerebral Vessels, *Arch. Neurol. & Psychiat.* **19**:1057 (June) 1928. Forbes, H. S., and Cobb, S.: Vasomotor Control of Cerebral Vessels, *Brain* **61**:221, 1938.

28. Talbot, J. H.; Wolff, H. G., and Cobb, S.: The Cerebral Circulation: VII. Changes in Cerebral Capillary Bed Following Cervical Sympathectomy, *Arch. Neurol. & Psychiat.* **21**:1102 (May) 1929.

29. Cobb, S.: The Cerebral Circulation: IX. The Relationship of the Cervical Sympathetic Nerves to Cerebral Blood Supply, *Am. J. M. Sc.* **178**:528, 1929.

30. Chorobski, J., and Penfield, W.: Cerebral Vasodilator Nerves and Their Pathways from the Medulla Oblongata, *Arch. Neurol. & Psychiat.* **28**:1257 (Dec.) 1932.

31. Volpitto, P. P., and Risteen, W. A.: The Use of Stellate Ganglion Block in Cerebral Vascular Occlusion, *Anesthesiology* **4**:403, 1943.

32. Hickcox, C. B.; Tovell, R. M.; Raskind, R., and Scoville, W. B.: The Stellate Ganglion: Its Significance in Practice, *Anesthesiology* **4**:150, 1943.

33. Burns, Shock, Wound Healing and Vascular Injuries, *Military Surgical Manuals*, National Research Council, Philadelphia, W. B. Saunders Company, 1943, vol. 5.

34. Leriche, R.: Les maladies des ligaturés: moyens de les prévenir et de les traiter, *Presse méd.* **48**:41, 1940.

35. Gage, M., and Ochsner, A.: The Prevention of Ischemic Gangrene Following Surgical Operations upon the Major Peripheral Arteries by Chemical Section of the Cervicodorsal and Lumbar Sympathetics, *Ann. Surg.* **112**:938, 1940.

36. Ochsner, A., and DeBakey, M.: Thrombophlebitis: Role of Vasospasm in Production of Clinical Manifestations, *J. A. M. A.* **114**:117 (Jan. 13) 1940; Therapy of Phlebothrombosis and Thrombophlebitis, *Arch. Surg.* **40**:208 (Feb.) 1940; footnote 15.

37. de Sousa Pereira, A., and Fontaine, R.: Edema duro post-traumatico curado por infiltracoes locais e do ganglio estrelado, *Portugal méd.*, 1936.

38. Flothow, P. G.: Diagnostic and Therapeutic Injections of Sympathetic Nerves, *Am. J. Surg.* **14**: 591, 1931. Marvin, H. M.: Surgical Treatment of Angina Pectoris, *Bull. New York Acad. Med.* **11**:453, 1935. Miller, H. R.: Angina Pectoris: Nerve Pathways, Physiology, Symptomatology and Treatment, Baltimore, Williams & Wilkins Company, 1939. Ochsner, A., and DeBakey, M.: The Surgical Treatment of Coronary Disease, *Surgery* **2**:428, 1937.

39. Mackenzie, J.: Diseases of the Heart, ed. 4, New York, Oxford University Press, 1925.

40. Swetlow, G. I.: Paravertebral Alcohol Block in Cardiac Pain, *Am. Heart J.* **1**:393, 1926; Angina Pectoris: Paravertebral Alcohol Block for Relief of Pain, *Am. J. Surg.* **9**:88, 1930.

Lundy,⁴² Seldon,⁴³ Woodbridge,⁴⁴ Levy and Moore⁴⁵ and Peterson⁴⁶) some favorable results have been obtained in the treatment of the cardiac pain of angina pectoris. Brown-Séquard paralysis following a paravertebral injection of alcohol for angina pectoris was observed in 1 case (Molitch and Wilson⁴⁷).

At present, I am using, in a systematic way, block of the middle cervical and stellate ganglions in all cases of angina pectoris for the purpose of establishing an indication for stellectomy. However, in the investigation of the pathways for painful sensations associated with angina pectoris, it must be remembered that blocking of the middle cervical and of the stellate ganglion is not sufficient. In cases of angina pectoris with coronary insufficiency I have observed the appearance of anginal crisis during blocking of the left middle cervical and stellate ganglions. In these cases immediate blocking of the left splanchnic nerves abolished the anginal crisis quickly. Since these observations, in all cases of angina pectoris in which repeated block of the middle cervical and stellate ganglions with procaine did not abolish or modify the anginal crisis, I have always blocked the splanchnic nerves, beginning with those on the left side. Within the limits of this experimental work, it was possible to find a few cases of angina pectoris in which block of the left middle cervical and stellate ganglions was not effective and a few cases in which block of the left splanchnic nerves abolished the crisis temporarily. Splanchnicectomy performed in these cases confirmed the indication furnished by the block.

41. Bland, E. F., and White, J. C.: Relief of Severe Angina Pectoris in Young People with Rheumatic Heart Disease, with Remarks on an Atypical Anginal Syndrome, *New England J. Med.* **215**:139, 1936: footnote 6.

42. Lundy, J. S.: *Clinical Anesthesia: A Manual of Clinical Anesthesiology*, Philadelphia, W. B. Saunders Company, 1944.

43. Seldon, T. H.: Regional Anesthetic Procedures Around the Vertebral Column, *Anesthesiology* **2**:669, 1941.

44. Woodbridge, P. D.: Therapeutic Nerve-Block with Procaine and Alcohol, *Am. J. Surg.* **9**:278, 1930.

45. Levy, R. L., and Moore, R. L.: Paravertebral Injections of Alcohol for the Relief of Cardiac Pain: A Review of Experience to Date and a Report of Nine Cases, *Arch. Int. Med.* **48**:146 (July) 1931; Paravertebral Sympathetic Block with Alcohol for the Relief of Cardiac Pain: Report of Forty-Five Cases, *J. A. M. A.* **116**:2563 (June 7) 1941.

46. Peterson, M. C.: Paravertebral Alcohol Injection for Cardiac Pain, *Anesth. & Analg.* **17**:35, 1938.

47. Molitch, M., and Wilson, G.: Brown-Séquard Paralysis Following a Paravertebral Alcohol Injection for Angina Pectoris, *J. A. M. A.* **97**:247 (July 25) 1931.

since the anginal crisis disappeared completely. These observations prove the existence of cases of angina pectoris in which stimuli arising in the solar plexus are transmitted along the splanchnic nerves, particularly on the left side, and reach the heart, through the cardiac branches⁴⁸ of the second, third and fourth thoracic sympathetic ganglions.⁴⁹ In these cases blocking of the middle cervical ganglion and of the stellate ganglion is insufficient to abolish the anginal crisis. Only associated blocking of the second, third and fourth thoracic ganglions, which White does, or blocking of the splanchnic nerves or splanchnicectomy, which I have done, abolishes the anginal crisis when stimuli which precipitate the crisis arise in the solar plexus.

In cases of facial paralysis of peripheral type, without anatomic lesions of the trunk of the facial nerve, repeated block produced favorable results. Also, in some cases post-traumatic paralysis of the radial and ulnar nerves⁵⁰ without anatomic lesions, even when it appeared several weeks after the accident, disappeared in a few weeks with repeated block of the middle cervical and stellate ganglions. The favorable results obtained in these cases must perhaps be interpreted as a consequence of improvement in the circulation of the trunk of the paralyzed nerve produced by block of the cervical sympathetic ganglions.

Block of the middle cervical and stellate ganglions has shown its usefulness as a therapeutic method in the relief of pain, as a means of analyzing the sympathetic conduction of pain and as a preoperative test for stellectomy in cases of thoracic pain and pain of the upper extremity and the head.⁵¹

In the syndrome of pain associated with trophic changes, known as causalgia (Mitchell⁵²), the pain results in arterial spasm, which intensi-

48. Kuntz, A., and Morehouse, A.: Thoracic Sympathetic Cardiac Nerves in Man: Their Relation to Cervical Sympathetic Ganglionectomy, *Arch. Surg.* **20**: 607 (April) 1930.

49. de Sousa Pereira, A.: A existencia fora do ganglio estrelado de vias simpaticas de innervacao cardiaca, *Reun. cient. Fac. med. do Porto*, January-March 1944.

50. de Sousa Pereira, A.: A influencia das infiltrações novocainicas repetidas do ganglio estrelado num caso de paralisia do nervo cubital, *Lisboa med.* **14**:1, 1937.

51. Davis, L., and Pollock, L. J.: The Role of the Sympathetic Nervous System in the Production of Pain in the Head, *Arch. Neurol. & Psychiat.* **27**:2-2 (Feb.) 1932.

52. Mitchell, S. W.: On a Rare Vasomotor Neurosis of the Extremities and on the Maladies with Which It May Be Confounded, *Am. J. M. Sc.* **76**:17, 1878.

fies the painful sensation.⁵³ In the early stages of this disease, block of the middle cervical and stellate ganglions may contribute to the relief of pain. In movements of the shoulder joint during the period following arthritis, arthrotomy or arthroplasty, block of the middle cervical and stellate ganglions relieves the sympathetic pain arising in the capsule and ligaments of the joint.

I am trying to determine the value of blocking the middle cervical and stellate ganglions to relieve the sympathetic pain arising from an operative wound in the thoracic viscera and to inhibit the sympathetic vasomotor reflexes which arise in the wound and contribute to the shock of the operation. It is known at present that with surgical trauma the vasoconstriction which is associated with disturbances such as pain is probably one of many factors in the genesis of shock (Blalock⁵⁴).

In cases of painful edema of the upper extremity,⁵⁵ observed immediately after amputation of the breast for cancer, with extirpation of the lymphatic nodes of the axilla, repeated blocks of the middle cervical and stellate ganglions cause the pain to disappear, with immediate vasomotor modification, rapid disappearance of the edema and prompt recovery of function of the extremity. In cases of pain associated with inoperable cancer of the mammary gland,⁵⁵ due to neoplastic lymphangitis, block of the middle cervical and stellate ganglions is followed by temporary disappearance of pain resulting from irritation of the sympathetic perivascular innervation. In these cases block of the middle cervical and stellate ganglions is especially important as a method of analysis of the mechanism of pain and as a preoperative test to define the indication for stellectomy.

SUMMARY

The vascular, neural and pleuropulmonary accidents observed in the course of stellate ganglion block, performed according to the technics

previously described, led to the study of a new technical method, the principal characteristics of which consisted in blocking, by means of a definite point of deep osseous reference, i. e., the transverse process of the sixth cervical vertebra, the middle cervical and stellate ganglions without any of the accidents which have been indicated.

From an experimental study of the technics already known, I was convinced that accidents would occur whenever the needle touched the stellate ganglion directly, whether the anterior, the anterolateral, the external or the supero-external approach was used.

This observation led me to study the topographic and anatomic relations of the stellate ganglion to the skeleton, to neighboring vessels, to the brachial plexus and to the pleura. From these investigations I deduced the possibility of obtaining, without accidents, block of the middle cervical, intermediate and stellate ganglions by means of descending infiltration anesthesia of these ganglions, with the needle inserted at the level of the base of the anterior surface of the transverse process of the sixth cervical vertebra. If, however, the anesthetic does not diffuse downward sufficiently to block completely the stellate ganglion, the needle must be inserted a second time and directed to the base of the transverse process of the seventh cervical vertebra, and the anesthetic must be injected close to the intermediate ganglion and the vertebral artery. In this manner, one can obtain a safe block of the middle cervical, intermediate and stellate ganglions.

Besides criticizing the several technics previously employed and describing the technic of stellate ganglion block with descending infiltration anesthesia, I have evaluated the signs which verify the physiologic interruption of the ganglions. The principal indications for employing either single or repeated blocks of the middle cervical and stellate ganglions as a diagnostic method, as a preoperative test for stellectomy or as a therapeutic method have been established.

Dr. A. Lamont, physician in charge of anesthesia at the Johns Hopkins Hospital, gave advice and encouragement in the preparation of this paper.

The Johns Hopkins Hospital, Baltimore.

53. Homans, J.: *Circulatory Diseases of the Extremities*, New York, The Macmillan Company, 1939.

54. Blalock, A.: *Principles of Surgical Care: Shock and Other Problems*, St. Louis, C. V. Mosby Company, 1940, p. 704.

55. de Sousa Pereira, A.: *A cirurgia da dor nos canceros do seio*, Inst. Portugues de oncolog., January 1944.

PROTEIN METABOLISM DURING CONVALESCENCE AFTER TRAUMA

RECENT STUDIES

JOHN EAGER HOWARD, M.D.

BALTIMORE

In the past several years many advances have been made in the field of protein metabolism. Under the stimulus of war especial interest has been directed toward protein metabolism after trauma of various sorts and during convalescence. The studies which will be summarized briefly here have, in the main, been carried out under the auspices of the Committee on Medical Research of the Office of Scientific Research and Development; many of them have been reported in an informal and preliminary manner at the Conferences on Metabolic Aspects of Convalescence, sponsored by the Josiah Macy Jr. Foundation.¹ At the outset it may be stated that the present state of knowledge leaves many problems yet unsolved, especially in regard to the mechanisms of the physiologic processes during periods of great wastage of nitrogen, when the organism consumes large portions of its vital tissue constituents in an effort to repair itself or to defend itself against injury.

The fundamental pattern of protein metabolism in healthy, vigorous persons subjected to injury may be illustrated by the chart of a patient covering from fracture of the tibia (chart 1). On a well rounded diet, with approximately 120 Gm. of protein and 3,000 calories per day, this patient lost about 200 Gm. of body nitrogen during the first thirty days after his injury. The average loss of nitrogen in a group of cases of fracture, which my associates and I observed, was 225 Gm. In terms of protein this amounts to more than 1,400 Gm., and in terms of muscle protoplasm, approximately 15 pounds (7 Kg.). The average duration of the phase of negative nitrogen balance was thirty-five days. The maximum

loss of nitrogen was not reached until six and six-tenths days (on the average) after the fracture occurred; the delay in reaching the peak of intensity was not due to slowed excretion of nitrogenous end products of protein catabolism, for the concentration of nonprotein nitrogen did not rise appreciably in the blood in this group of cases. After the nitrogen balance was reached (on an average of thirty-five days after fracture was sustained), recovery of lost nitrogen was slow; in the succeeding month or more the patients, lying in bed in casts, regained but a small

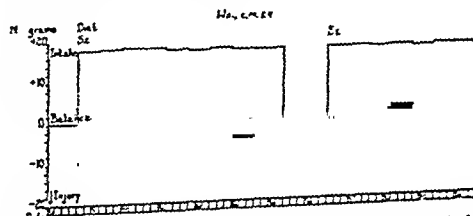


Chart illustrating the pattern of protein metabolism in a Negro woman aged 24 recovering from fracture of the femur (Howard, Parson, Stein, Eisenberg and Reidt²).

percentage of the nitrogen which they had lost during the phase of negative nitrogen balance.²

Operative cases (femoral osteotomy) were studied in a similar manner; the same pattern was shown qualitatively, but there was a much shorter phase of nitrogen loss (an average of only nine days); the losses of nitrogen were much smaller, averaging but 45 Gm., and in the subsequent periods these losses were rapidly restored.³

These movements of nitrogen after fracture and osteotomy confirm the observations of Cuthbertson, which are summarized in his Arris and Gale Lecture of 1942.³ Similar observations were made on patients during convalescence after fractures by Browne, Stevenson and Schenker.⁴

From the Department of Medicine of the Johns Hopkins University School of Medicine and the Johns Hopkins Hospital.

Read at a joint meeting of the Section on Medicine and the Section on Surgery of the New York Academy of Medicine, Jan. 16, 1945.

1. Minutes of the Conference on Metabolic Aspects of Convalescence Including Bone and Wound Healing, New York, Josiah Macy, Jr., Foundation: (a) Fifth Meeting, Oct. 8-9, 1943, p. 50; (b) Sixth Meeting, Feb. 11-12, 1944, p. 151; (c) p. 156; (d) p. 67; (e) Fifth Meeting, Oct. 8-9, 1943, p. 57; (f) Fourth Meeting, June 11-12, 1943, p. 113; (g) p. 22; (h) Seventh Meeting, June 9-10, 1944, pp. 117 and 120.

2. Howard, J. E.; Parson, W.; Eisenberg, H.; Stein, K. E., and Reidt, V.: Studies on Fracture Convalescence: I. Nitrogen Metabolism After Fracture and Skeletal Operations in Healthy Males, *Bull. Johns Hopkins Hosp.* 75:156, 1944.

3. Cuthbertson, D. P.: Post-Shock Metabolism: Response (Arris and Gale Lecture), *Lancet* 1:453, 1942.

and by Albright and Reifenshtein.^{1b} Types of trauma other than fracture and osteotomy, have produced this same general pattern of destruction of protein. It has been found in patients after burns by Browne;^{1c} in patients with various types of infection, including meningitis and virus pneumonia, by Peters;⁴ in patients with empyema and wounds of the chest by Browne,^{1a} and in patients suffering from induced malaria by Howard and Bigham.⁵

The known facts regarding this fundamental pattern of increased destruction of protein may be summarized as follows:

1. The nitrogen deficit is brought about by increased excretion of nitrogen in the urine. It has repeatedly been shown that, unless complicating gastrointestinal lesions occur, there is no more than a normal amount of nitrogen in the stools; hence, the reaction does not involve an abnormality in the intestinal absorptive mechanism.²

2. Urinary nitrogen is mostly in the form of urea.³ Normally, urea (urea plus ammonia) constitutes 80 to 90 per cent of the urinary nitrogen; in the reaction here under consideration, when as much as 40 or 50 Gm. of nitrogen was excreted per day in the urine, urea and ammonia accounted for 85 per cent or more of the nitrogen. Excretion of creatinine was unchanged, excretion of creatine was slightly increased in cases of fracture, as might be expected, and excretion of uric acid was only slightly greater than normal.³ One might conclude from this observation that disposition of the nitrogenous portion of catabolized protein after trauma follows the same pattern as in health.

3. Fever per se will not account for the reaction. Many of our patients with fractures were free of fever. Patients with malaria excreted far more nitrogen than could be accounted for by a 7 per cent increase in total metabolism for each degree of elevation of temperature.⁶ Furthermore, as will be evident later, certain patients may have fever of considerable magnitude

and yet not exhibit any increase in protein metabolism. I do not mean to imply that infections and other conditions causing fever do not promote and exaggerate protein catabolism, for it is my co-workers' and my conviction that they do.⁷

4. Sulfonamide drugs had no effect per se on the reaction, either in altering the intensity of the protein catabolism or in bringing about any change in the absorption of foodstuffs.² My associates and I do not include in this category, of course, toxic reactions to the sulfonamide compounds, on which we have no data. Furthermore, it is our belief that, in their capacity to reduce the manifestations of infection, sulfonamide drugs would have the effect of reducing the intensity of protein catabolism.

5. Atrophy of disuse will account for only a small part of nitrogen loss.⁸ Patients immobilized in casts after osteotomy were subjected to exactly the same "disuse" as were those with fracture; yet the quantitative aspects of the picture of protein metabolism were very different in the two groups.

6. Protein metabolism in healthy, vigorous patients after trauma differs from that during simple starvation. In starvation protein stores are called on presumably to furnish fuel and other metabolic needs of the organism. After a brief initial period of starvation, during which glycogen stores are utilized and but little nitrogen is lost, there is a steady loss of nitrogen, amounting to about 10 Gm. per day in an average-sized man.⁹ This loss of nitrogen can be appreciably reduced by feeding carbohydrate, and quickly stopped by giving a diet which provides adequate calories and protein. But it has been found that in healthy persons after trauma high caloric diets, with large quantities of protein, often do not appreciably spare the body nitrogen at the height of a vigorous protein catabolism reaction whether the protein is administered orally, as highly nutritious food,¹⁰ or intravenously, as amino acids.¹ There is certainly some nitrogen-sparing effect of such therapy during mild reactions and during the periods of waxing and waning of the vigorous reactions; yet the effect is strikingly different in degree from the reversal of loss of nitrogen obtained with similar therapy in cases

4. Peters, J. P.: Problems of Nitrogen Metabolism. *Federation Proc.* 3:197, 1944.

5. Howard, J. E., and Bigham, R. S., Jr.: Unpublished data.

6. It might be argued that the destruction of red blood cells associated with malaria should be taken into account; on the other hand, the protein content of such cells should, under normal states, be available for reutilization and the over-all nitrogen balance thus be relatively unaffected (Rohsheit-Robbins, F. S.; Miller, L. L., and Whipple, G. H.: Hemoglobin and Plasma Protein: Simultaneous Production During Continued Bleeding as Influenced by Amino Acids, Plasma Hemoglobin and Digests of Serum, Hemoglobin and Casein, *J. Exper. Med.* 77:375, 1943).

7. Howard, J. E.; Winternitz, J.; Parson, W.; Bigham, R. S., Jr., and Eisenberg, H.: Studies on Fracture Convalescence: II. The Influence of Diet on Post-Traumatic Nitrogen Deficit Exhibited by Fracture Patients, *Bull. Johns Hopkins Hosp.* 75:209, 1944.

8. Howard and others.² Cuthbertson.²

9. Benedict, F. G.: A Study of Prolonged Fasting. Publication 203, Carnegie Institute of Washington, 1915.

10. Howard and others.² Cuthbertson.² Peters.⁴

of simple starvation. Plasma protein, however, does seem to act as an efficient nitrogen-sparing agent¹⁰ in cases so far studied, even with vigorous protein catabolism; this fact should be taken into account in any theoretic consideration of the mechanism of the reaction.

Another way in which the protein catabolism reaction after trauma differs from that due to starvation is in the behavior of potassium. In starvation, after the initial large output of potassium that presumably accompanies utilization of glycogen, the losses of nitrogen and potassium remain constant, at a ratio of approximately 10:1, which is the proportion in which these substances occur in muscle protoplasm.¹¹ However, during vigorous protein catabolism after fracture, when the patient is adequately fed, there has been observed no coincident loss of potassium, but often a positive potassium balance, even during the periods of greatest loss of nitrogen.¹²

7. All patients do not react alike to what is apparently the same stimulus. Considerable variation was observed in the magnitude of the loss of nitrogen in our studies on fracture. In an emaciated patient, the nitrogen balance was maintained even on a low intake of protein.¹² Peters likewise found that nitrogen equilibrium could be maintained in some patients suffering from acute infections with comparative ease, though most patients had large losses of nitrogen, which could not be prevented by feeding a diet high in protein.⁴ Browne pointed out that after a long chronic illness it was a simple matter to maintain nitrogen equilibrium in a patient, even with continuing fever; in fact, strong positive nitrogen balances were effected in his chronically ill patients with high calories and protein.¹⁰ Co Tui maintained nitrogen equilibrium, and even positive nitrogen balance in his patients with chronic gastric lesions after extensive surgical procedures.¹⁰ The patients with malaria observed by Howard and Bigham seemingly responded to early chills with more vigorous protein catabolism than to later chills of apparently similar severity.⁵ Cuthbertson found that rats previously starved of protein did not lose nitrogen after fracture while normally fed rats invariably did.¹² From these observations it must be concluded that the capacity to respond to trauma with increased breakdown of protein is a variable factor, being great in some subjects and reduced or practically absent in others.

H. Fenn, W. O.: Potassium in Physiological Processes, *Physiol. Rev.* 20:377, 1940.

12. Howard, J. E.: Metabolic Observations on Patients Convalescent from Fractures, *Tr. A. Am. Physicians*, 1944, to be published.

COMMENT

These, then, are the main facts that have so far come to light in regard to the protein catabolism reaction after various sorts of injury. Though one is hardly in a position now to make any sweeping conclusions as to either the mechanism of the reaction or its therapeutic implications, it is perhaps desirable to reflect and make a few tentative deductions.

Judging from the magnitude of the nitrogen losses under consideration in this discussion, the main source of the lost nitrogen must be the body tissues—the protein of the cells. Some cells have doubtless furnished proportionately much more nitrogen and some much less than others. In all likelihood the same “available” nitrogen stores are called on and sacrificed in this reaction as were used to replenish plasma protein when this element was constantly removed from dogs in Whipple and Madden’s classic experiment.¹³

It seems hardly worthy of argument that a person is better off before his nitrogen stores have been wasted than after. Surgeons have long noted that chronically debilitated patients are poor operative risks. Mulholland and associates reported that their patients whose stores of protein were depleted experienced quick healing of decubitus ulcers when they were given large amounts of amino acid.¹⁴ Patients with burns respond much better to skin grafting after their nitrogen stores have been replenished.¹⁵ The dogs used in Whipple and Madden’s experiment which were depleted of protein were poorly resistant to all sorts of injurious agents, as compared with normal dogs.¹³ In the case of susceptibility of liver to chloroform poisoning, the most important absent factor proved to be methionine, and replacement of this single element restored hepatic resistance to normal.¹⁶ Time may reveal specific defects of this or other amino acids in other instances of increased susceptibility to toxic agents. It may be that in the protein catabolic response to injury the organism is really seeking an excess of one or more specific amino acids. Administration of amino acids.

13. Whipple, G. H., and Madden, S. C.: Hemoglobin, Plasma Protein and Cell Protein: Their Interchange and Construction in Emergencies, *Medicine* 23:215, 1944.

14. Mulholland, J. H.: Co Tui, Wright, A. M., Vinci, V., and Shafiroff, B.: Protein Metabolism and Bed Sores, *Ann. Surg.* 118:1015, 1943.

15. Madden, S. C.: Personal communication to the author, to be published.

16. Miller, J. L., and Whipple, G. H.: Liver Injury, Liver Protection and Sulfur Metabolism, *J. Exper. Med.* 76:421, 1942.

individually and in groups, and study of excretion of specific amino acids during the post-traumatic state (as is being carried out on normal persons by Holt and Albanese) may provide the answer to this question. At any rate, it seems justifiable to conclude for the present that, other things being equal, full nitrogen stores are a valuable asset to the resistance of the organism and that prevention of depletion of such stores and repletion of them if lost are worthy of therapeutic efforts.

It is clear also, from the foregoing comments, that the capacity to respond to injury with increased breakdown of protein is an asset to the organism. It is the healthy, vigorous, well fed patient who responds to a given injury with the greatest breakdown of protein. It does not necessarily follow that his wound will heal faster or resist infection better, for many other factors enter into recovery and return to fitness. Nevertheless, in the present state of knowledge, a wise patient should prefer to possess the capacity to respond with large losses of nitrogen. He should like, also, to have his cellular stores kept replete with nitrogenous components for maximal efficiency in whatever duties they might be called on to perform—provided that, in the keeping of them thus stored, no more important functional elements of the body are sacrificed.

Many more data are needed before categorical answers can be given to the questions of how much protein to administer, and when and how. When time is not at a premium, the refilling of protein stores should render the protein-depleted patient a better surgical risk. During convalescence repletion of lost protein should also improve his status. Since it is usually easiest to achieve a positive nitrogen balance in persons who have lost large amounts of body protein, administration to such patients of high protein diets before operation and as soon afterward as is practicable is clearly indicated. In instances in which, owing to a pathologic condition in the gastrointestinal tract or elsewhere, oral ingestion of a high protein diet is impossible, amino acids or plasma proteins may be administered by vein, with considerable benefit.

It was previously pointed out that in a vigorous reactor, at the height of an intense reaction, even large amounts of nitrogen, fed as protein food or given intravenously as amino acid, fail to spare to any appreciable degree the nitrogen waste. It has been my experience that healthy, vigorous patients rarely have much appetite at such a time and forced feeding, either by persuasion or by stomach tube, is utterly impractical, and usually impossible. Furthermore, forced peroral feeding to sick patients may well

tend toward embarrassment of the circulation by promoting acute gastric dilatation. Forced oral feeding of these patients may thus be injurious, as well as fail to spare body protein. It would perhaps be wiser to give the bare maintenance protein and caloric requirements by intravenous administration of dextrose, amino acids and plasma and to feed higher protein diets later, after the greatest intensity of the protein catabolism has waned. In emergency operations on patients whose protein stores are depleted and to whom further losses of nitrogen would presumably be most harmful, mixtures of amino acids, given intravenously during the early periods after operation or injury, have proved most helpful.^{1a} Fortunately, too, these patients are the ones in whom positive nitrogen balance is easily induced. During intravenous administration of a protein hydrolysate Howard and Bigham noted that the serum nonprotein nitrogen rose to 70 mg. or more per hundred cubic centimeters, presumably most of this nonprotein nitrogen being amino nitrogen, for the serum urea concentration remained normal.² No harmful effects were noted from the elevation of nonprotein nitrogen, and there was a rapid fall to normal with cessation of the therapy.

Concerning the fundamental nature and mechanism of the protein catabolism reaction there is as yet no knowledge. From the types of situations in which the reaction has been found, one is tempted to guess that the stimulus to its production is probably in some way associated with the absorption of the products of devitalized tissue. The capacity to respond to the stimulus seems closely associated with the amount and availability of body protein. However, that it is simply a matter of the degree of fullness of the warehouses of protein is unlikely. There may be required an intermediary factor, such as a principle of the adrenal or the pituitary gland, as suggested by Albright and Browne.^{1c} Indeed, Venning found increased quantities in the urine of a substance capable of promoting gluconeogenesis in adrenalectomized rats during convalescence from injury.^{1b} It is my impression, derived from observations in this group of cases, that administration of large quantities of protein is the most effective way so far found of prolonging the protein catabolism reaction; conversely, undernutrition is the most effective way of shortening it. These observations may be important when it is learned whether a large protein turnover is helpful or harmful to rapid repair and convalescence in general.

Finally, of course, many factors other than protein metabolism are of greatest importance in the over-all picture of convalescence. The cir-

culatation, the fluids of the extracellular compartment in which the cells are bathed and many other physiologic factors, including availability of necessary vitamins, must be in the most desirable state for the cells to function at their maximal efficiency.

SUMMARY AND CONCLUSIONS

Traumas of a wide variety increase protein metabolism. In reactions of great magnitude

there may be extensive wastage of nitrogen and great losses of body protein. The vigor of the protein catabolism depends on two factors: (1) the intensity of the stimulus and (2) the capacity of the organism to respond to the stimulus. The stimulus may be related to the absorption of devitalized tissues; the capacity to respond appears, to some degree at least, to be related to the previous state of protein nutrition.

The Johns Hopkins Hospital.

USE OF OMENTUM TO CLOSE PERFORATIONS OF THE STOMACH

PHILIP B. PRICE, M.D., AND TUNNIE F. LEE, M.D.

SALT LAKE CITY

It is common practice to cover perforated ulcers of the stomach with tabs of omentum, especially when the adjacent gastric wall is too indurated and friable for satisfactory closure of the hole with sutures alone. Free omental transplants, or grafts, have been recommended for that purpose, and illustrations of such an operation may be found in current surgical textbooks.

On theoretic grounds it may be questioned whether this procedure is sound surgical practice. One might expect the free transplants, deprived temporarily of a blood supply, to be susceptible both to the digestive action of gastric juice and to infection, which is sure to be present, at least part of the time. In that case the safer procedure would be to cover the defects only with living omentum, which presumably would offer greater resistance to both digestion and infection.

EXPERIMENTAL PROCEDURE

We have studied this problem experimentally by means of operations on dogs.

Healthy stock animals were used. With the dogs under light anesthesia induced with pentobarbital sodium, and with aseptic technic, round or oval holes were cut in the anterior gastric wall. These artificial perforations were then covered with omentum in various ways. The holes were deliberately made larger than the perforations encountered clinically because we wished to subject the covering omentum to relatively severe tests, and also because small holes in the normal gastric wall heal too rapidly to present the problems posed by the more slowly healing perforations of peptic ulcer. Cotton thread was used for sutures and ligatures. All the animals were allowed water and food (dog pellets) ad libitum after operation. Surviving animals were subjected to exploratory operation or were killed after various intervals, in order to study the process of repair.

PROTOCOLS

The experiments performed and the results observed are indicated in the following protocols:

A. Hole Covered with Living Omental Patch.—1. A large hole, 3 by 4.5 cm., was cut in the anterior gastric wall. After bleeding had been stopped, the hole was covered with a double thickness of omentum. Interrupted sutures around the margins anchored the patch

in place. This omentum, as is so often the condition in dogs, was poor in fat and in places appeared extremely thin and delicate. Peritonitis did not develop, but the animal seemed unwell and lost considerable weight. After twenty-one days the dog was killed. The patch, now thick and fibrosed, was tightly adherent to the site of the stoma. From the gastric side the hole appeared as a shallow crater, 1 by 1 cm. Microscopic sections showed sluggish proliferation of gastric epithelium, extensive and dense fibrosis of the omental patch and, at the surface of the crater, a layer of hyalinization, necrosis and sloughing.

2. An even larger hole, 3 by 6 cm., was made in the anterior gastric wall. A sample of fasting gastric contents taken at this time showed 23.4 units of free acid and 34 units of total acid. The hole was covered with a double layer of omentum, as just described. Peritonitis did not occur; the dog remained healthy and gained weight. The animal was killed after one hundred and five days. The omental patch appeared densely fibrosed and adherent. The gastric defect had almost healed, a small crater remaining. Histologic examination revealed superficial inflammatory reaction, necrosis and sloughing of the surface of the crater and dense fibrosis of the underlying omentum, extending to a depth of about 1 cm., at which level normal fat was encountered.

B. Hole Covered with Free Omental Patch.—1. A hole, 1.5 by 2 cm., was covered in the manner previously described with a double layer of omentum, but the patch was then cut free from the parent omentum. Gastric contents contained 30 units of free acid and 42.5 units of total acid. The animal died within twenty-four hours with general peritonitis. Necropsy showed that the patch was entirely necrotic and leaked like a sieve.

2. Method 1 was repeated. The hole was 1.5 by 1.5 cm. The dog used in this experiment likewise died within twenty-four hours with general peritonitis. The patch was necrotic, with multiple perforations.

3. A hole, 2 by 2 cm., was covered as before with a free patch of omentum. This patch also became necrotic, and the dog died with peritonitis.

C. Hole Stopped with Living Tab of Omentum.—1. A hole, 1 by 1 cm., was cut. A tongue of omentum was drawn up over the defect and was fastened lightly in place with overlying mattress sutures. Exploration after twenty-four hours showed that there had been no leakage. Grossly the omentum adherent to the hole appeared normal, but microscopically there was a superficial inflammatory reaction where the plug had been exposed to the action of gastric juice.

2. A hole, 1 by 1.5 cm., was similarly covered with a tongue of living omentum. The dog, which remained well, was killed after eight days. The omental plug was tightly adherent and fibrosed. There had been no leakage. Microscopic examination showed beginning proliferation of gastric epithelium at the margins of the crater, with acute inflammatory reaction and fibrosis of the plug generally. Near the surface of the crater

From the Department of Surgery, University of Utah School of Medicine.

Aided by grants from the Rockefeller Fluid Research Fund and the Doctors' Research Fund.

there were hyalinization and sloughing of necrotic material into the lumen of the stomach.

3. A hole, 0.5 by 1 cm., was covered as before with a tab of living omentum. The dog remained healthy and was killed after sixty-one days. Gross and microscopic examination revealed a fibrosed tab of omentum, but the gastric defect had healed, with complete epithelization.

4. A hole, 2.5 by 3 cm., was covered with a tongue of living omentum. The dog remained vigorous and healthy. After fifty-seven days exploratory operation revealed a living, fibrosed, adherent plug, completely covered with regenerated tissue of the gastric wall.

D. Hole Stopped with Free Tab of Omentum.—1. A hole, 2 by 2 cm., was covered in the manner just described with a tongue of omentum, which was fastened with five looping mattress sutures. The parent omentum was cut free. General peritonitis developed, and the dog died in less than twenty-four hours. The plug was necrotic, permitting leakage of gastric contents. The adjacent gastric mucosa had an irregular zone of necrosis, and at one place the gastric wall had perforated spontaneously.

2. A transverse ellipse, 3.5 cm. long, was covered with a free tongue of omentum. Local, then general, peritonitis developed, and the dog died twelve days after operation. The plug was entirely necrotic. Extensive adhesions represented unsuccessful efforts of the parent omentum and the intestine to wall off the infection. The gastric defect showed no evidence of healing.

3. A hole, 1.5 by 1.5 cm., was stopped with a free tab of omentum. The animal survived and was killed after eight days. Grossly the omental tab appeared necrotic, perforation and peritonitis having been averted by the parent omentum, which overlay the plug and was tightly adherent to the stomach. Microscopically there were active proliferation of the marginal gastric epithelium, necrosis and multiple abscesses throughout the plug and an inflammatory reaction, with fibrosis, in the adjacent parent omentum.

4. An oval hole, 0.5 by 1 cm., was covered with a free tab of omentum. The dog, which remained healthy, was killed after sixty-one days. Both grossly and histologically the plug showed multiple abscesses and necrosis, perforation having been averted by the protective action of the adherent parent omentum. The gastric stoma had nearly healed, however, by fibrous constriction and epithelial proliferation.

5. A hole, 3 by 3.5 cm., was covered as before with a free omental graft. The dog remained healthy and was examined after fifty-seven days. The omental plug was densely fibrosed but was living. The gastric defect had partly healed. Microscopic section showed that the plug was receiving a rich new blood supply from the parent omentum, which overlay it.

6. Two oval openings in the anterior gastric wall were each covered with a free tab of omentum; the parent omentum was then excised, so as to eliminate the protective action demonstrated in the preceding experiments. The dog remained well and was killed after fifteen days. Both tabs were fibrotic and contained numerous microscopic abscesses. The gastrosplenic ligament had come up to cover the grafts, thus averting probable perforation and peritonitis.

E. Unsutured Gastric Incision Covered with Free Omental Graft.—1. A transverse incision in the anterior gastric wall was not sutured, but it was covered with a free omental graft, which was fastened lightly in place with over-arching sutures. The dog, which remained healthy, was killed after twenty-one days. The adherent omental tab was somewhat fibrosed but living; it con-

tained no abscesses. It was not adherent to the parent omentum or to any surrounding structures; its new blood supply apparently came entirely from the gastric wall. The gastric incision was shown by microscopic section to have healed completely, with minimal inflammatory reaction.

2. Procedure 1 was repeated. A transverse incision, 2 cm. long, unsutured, was covered with a free tab of omentum. Analysis of the gastric contents (fasting) showed 37.1 units of free acid and 67.2 units of total acid. The animal remained healthy and was subjected to exploratory operation after ten days. The site of the graft was adherent to the liver and the anterior abdominal wall. The graft itself was indurated and inflamed. The gastric incision appeared healed.

Résumé of Experimental Results.—A. Large Hole Covered with Living Omental Patches:

For this experiment 2 dogs were used; both survived. The gastric defects healed slowly over the patches, which were greatly thickened and fibrosed but which showed only superficial necrosis and sloughing at the gastric surface.

B. Smaller Holes Covered with Free Omental Patch: Three dogs were used for this experiment; all died with general peritonitis. All the grafts were necrotic, with multiple perforations.

C. Hole Stopped with Tab of Living Omentum: None of the 4 dogs used for this experiment died. All the plugs showed fibrosis, acute inflammatory reaction and superficial necrosis where they were exposed to the action of gastric juice.

D. Hole Stopped with Free Tab of Omentum: Six dogs were used for this experiment; 2 died with general peritonitis from necrosis and perforation of the grafts; in 3 of the 4 living animals the plugs were largely necrotic and perforation and peritonitis probably been averted only by the protective action of parent omentum and adjacent structures lying off the grafted area. Only one of the grafts lived and proved to be an effective barrier; this graft had received a rich blood supply from the parent omentum.

E. Unsutured Gastric Incision Covered with Free Omental Graft: Both dogs survived this procedure. The grafts showed no inflammatory reaction but lived; owing to rich circulation from adjacent tissues. They had healed promptly.

COMMENT

It is clear from these experiments that patches or tabs of omentum may be used to cover defects, and even large holes of dogs. These seals become firm and resist infection and digestion and leak. Free omental transplants, however, are liable to infection, necrosis, and they tend to perforate, with result-

peritonitis. In several instances peritonitis was averted by the protective action of the parent omentum, but in such cases it would be more sensible and safer simply to seal the holes with living omentum at operation.

Although these experiments on healthy canine stomachs do not reproduce exactly the situation in perforated gastric ulcers, they do suggest that living omental or mesenteric tabs can be used to cover these defects with less risk than is involved with free transplants of omentum.

SUMMARY

Living omental patches or tabs were used successfully to cover relatively large holes in the

stomachs of dogs. Such seals appeared to be highly resistant to digestion and infection, giving the gastric defects time to heal.

Free omental transplants similarly employed, being temporarily without any blood supply, are susceptible to infection and the corrosive action of gastric juice. Necrosis and perforation of the graft occurred in many instances.

These experimental results suggest that in clinical surgical procedures it is more rational and safer to use living tissue than free omental grafts to cover perforated gastric ulcers or to reenforce lines of anastomosis.

University of Utah School of Medicine.

CYSTS OF THE URACHUS

C. F. SAWYER, M.D.

CHICAGO

The allantois is a fetal membrane which develops from the hindgut. Externally it helps to form the placenta and umbilical cord, and internally the urinary bladder develops as a dilatation of its distal end.

The intra-abdominal portion of the allantois, between the umbilicus and the bladder, is the urachus. In normal development this remains as the middle umbilical ligament, which is a cord passing from the apex of the bladder along the posterior surface of the anterior abdominal wall to the umbilicus.

In a small number of cases the obliteration of this canal is not completed at birth, and several types of anomaly may result. The condition has been discovered twice as often in males as in females. It is probably most frequently found in infants at birth or after separation of the umbilical stump. It may first manifest itself in the baby as some form of irritation about the navel. This has been called the congenital type, as opposed to the so-called acquired type, discovered later in life. This distinction, however, like the use of the same terminology in classifying inguinal hernias, is misleading. All pathologic conditions of the urachus are basically congenital. No doubt there are many instances of patent urachus which, because of lack of symptoms, are never discovered.

Vaughan¹ classified the types of patent urachus as follows: (1) the canal which is open all the way from the umbilicus to the bladder; (2) the duct which is closed at the bladder but open at the umbilicus; (3) the urachus which is closed at the umbilicus but opens into the bladder; (4) the "blind" type, in which both the umbilical and the vesical end are closed but some intervening part or parts of the duct remain open.

Types 1 and 2 account for the formation of fistulas, although because of infection the other types may form fistulas also. The "blind" type is responsible for the development of urachal cysts. Colston² stated that the secretory activity

of the epithelial membrane which lines the pocket or canal may produce a cyst at any age. Even if not primarily infected, such an accumulation is prone to become so, and many things may happen. Desquamated epithelial debris may partially or completely block the canal. The epithelial lining of the canal or of a subsequent cyst may be more or less completely destroyed by persistent infection. At the same time the fibrous tissue wall of the canal or the cyst will be greatly increased by the same process. Most of these cysts are small and confined to the anterior abdominal wall at or near the midline. Their clinical course has been compared with that produced by a pilonidal cyst.

Through chronic exudation and retention over a considerable period, some of these cysts may increase greatly in size and invade the abdominal cavity. Some will be the size of an orange or grapefruit, but several cases have been reported in which a mistaken diagnosis of ovarian cyst, ascites or even pregnancy has been made. Peritonitis due to rupture of a large urachal cyst has been described, and there are reports of formation of fistulous tracts with ovarian and dermoid cysts. The development of a malignant growth, which is likely to involve the bladder early, has been mentioned in the literature several times. This complication may come with either a small or a large cyst.

The distortion produced by a large cyst of the urachus may make an accurate diagnosis as to its origin difficult. This is especially true if there is an entire absence of suggestive history. In the reports on large cysts there is little or no evidence of previous symptoms pertaining to the bladder. The topographic relationships of a large urachal cyst and its location and point of attachment to the apex of the bladder, which are revealed at operation, must be relied on in making the diagnosis. If the epithelial lining has been destroyed, there will be no distinctive or characteristic features of the wall of the cyst, either macroscopic or microscopic, which will verify its origin.

REPORT OF A CASE

C. E. M., a white man aged 64, a railroad official, married, with two grown sons, entered the hospital

1. Vaughan, G. T.: Patent Urachus, *Tr. Am. S. A.* 23:273-294, 1905.

2. Colston, J. A. C.: The Urachus, in Nelson Loose-Leaf Living Surgery, New York, Thos. Nelson & Sons, 1928, vol. 6, chap. 6, p. 373.

on Nov. 10, 1942 for examination. At irregular intervals for several years he had had attacks initiated by a slight chill, followed by fever and general malaise. The attacks were sometimes, but not always, associated with intestinal disturbance. There was some abdominal soreness but not much pain. The attacks were unrelieved by bowel movements and lasted one or two days. In the last year there had been increasing abdominal distress, which was not always associated with these attacks. The distress seemed to be intestinal rather than gastric, but it had no particular pattern. Frequently it did not seem influenced by the type of food eaten. There were distention and soreness in the lower portion of the abdomen. The history suggested a spastic colon but was not always consistent with the usual findings. He was not constipated, and no blood had been noted in the stools. He had lost over 15 pounds (6.8 Kg.) in the last year, with a decrease in strength and general well-being.

He was a well built man, being over 6 feet (180 cm.) in height and normally weighing about 200 pounds (91 Kg.). Examination of the abdomen showed some general distention and a slightly movable mass to the left of the midline in the left lower quadrant. There was little local tenderness. Proctoscopic examination gave no evidence of a pathologic process. Fluoroscopic



Fig. 1.—Roentgenogram (Nov. 11, 1942) showing the colon filled with barium sulfate, some of which has passed through the fistula into the cyst.

examination, made immediately after administration of an enema of barium sulfate, revealed marked spasm in the lower portion of the colon; but after five minutes the entire colon filled to its capacity, and on the median side of the sigmoid small quantities of the emulsion entered a diverticulum the size of a grapefruit. Roentgenograms made after evacuation revealed some retention of barium in the colon and in the diverticulum. They further showed several small diverticula of the sigmoid. Roentgenograms taken twenty-four hours later showed the large diverticulum in both anteroposterior and lateral projections. They revealed it to be nearly empty and in a position adjacent to the anterior abdominal wall. The Kahn reaction of the blood was negative. There were 3,800,000 red blood cells, 10,000 white cells and a hemoglobin content of 78 per cent. The urine and the stools were normal.

Operation was advised but not submitted to at this time. The patient was placed on a careful bland diet and observed frequently. For the following nine months he continued to function at his office about half the time but was never well, and all previous symptoms became slightly aggravated.

He reentered the hospital on Aug. 17, 1943, and roentgenographic and other check-up examinations were

repeated, with similar results. He had lost 15 more pounds (6.8 Kg.), and the diverticulum seemed slightly larger. At operation, on August 21, an incision 7 inches (18 cm.) in length was made slightly to the left of the tumor mass. The presenting cystic tumor was somewhat movable laterally but not in a superior-inferior direction. It was lying just beneath the anterior abdominal wall, with the cystic, or larger, part of the mass in a superior position, while medially and inferiorly it was continued as one structure, tapering down to a firm ropelike pedicle, 4 cm. in diameter. This became somewhat flattened and fanned out below to be firmly attached to the apex of the bladder and the anterior abdominal wall. The cystic mass was roughly spherical, with diameters varying from 10 to 14 cm. Approximately three fourths of the entire outer surface was free and smooth, with a normal-appearing peritoneal covering. A considerable area of the left lateral and posterior surface of the cyst was closely adherent to the sigmoid. This was dissected free to the point where a fistulous tract existed between the inside of the cyst and the lumen of the sigmoid. The



Fig. 2.—Roentgenogram (Aug. 18, 1943) showing a somewhat larger cyst and the passage of more barium through the fistula.

fistula was doubly clamped and severed, and the side next the sigmoid was satisfactorily repaired. The fistulous opening into the cyst was several centimeters distant from the solid, or pedicle, portion of the mass. Severing this firm structure allowed the removal of the cyst. It did not seem to contain a channel or canal, and, although there was a definite blood supply, the pedicle was for the most part like the wall of the cyst itself, densely fibrous. Sulfathiazole was sprinkled into the field and a Penrose drain inserted before closure.

The patient made an excellent recovery, without infection or other major complications. He had a good bowel movement on the sixth day postoperatively and fairly regular movements thereafter. He left the hospital on September 9 and continued to improve. He has had no serious symptoms since and has completely regained his weight, strength and general health.

The contents of the cyst consisted of fairly fluid, pale brownish red, foul-smelling material. The interior was lined by pale reddish gray to light brownish or grayish

tan tissue, which was extensively mottled with darker red. This lining measured up to 2 mm. in thickness and in areas had a coarsely mamillated appearance. The remainder of the wall of the cyst consisted of fairly dense, firm, grayish white fibrous tissue, measuring up to 0.7 cm. in width in areas. Microscopic examination revealed that dense fibrous tissue presenting pronounced chronic inflammation constituted the wall of the cyst. The interior was lined by granulation tissue with chronic inflammation. At the site of its detachment from the colon only was there noted a mucus-secreting colonic type of mucosa.

COMMENT

This cyst was believed to have been urachal in origin because of its anatomic relations. Its connection with the colon was thought to be incidental. The adjacent colonic wall showed in the roentgenogram small diverticula of the usual

type; one may surmise that a perforation had occurred from the presence of one adjacent to the wall of the cyst, with resulting local peritonitis and eventual formation of the fistula. It is thought that a cyst or a diverticulum, either congenital or acquired, originating from the colon would have produced a more abrupt clinical episode in its incipency, would have been found at operation to have less free, nonadherent surface and would have shown some gross or microscopic indications of its origin. It was evident that the large thick pedicle of this cyst contained an adequate blood supply for survival of the cyst, while the fistulous tract and adjacent adhesions lacked sufficient vascularity for survival of so large a mass.

1525 East Fifty-Third Street.

PROPHYLAXIS OF WOUND INFECTION

STUDIES WITH PARTICULAR REFERENCE TO SOAPS AND IRRIGATION

L. W. PETERSON, M.D.

CHICAGO

Since the time of Lister, the local care given wounds—particularly from the standpoint of prophylaxis of infection—has been the center of much medical discussion. Naturally, the type of therapy used will be influenced by such factors as the degree of contamination, the length of time since injury and the location, type and extent of injury.

Various antiseptics, as they have been discovered, have been used in wounds as easy substitutes for cleansing. It was learned long ago that antiseptics strong enough to destroy bacteria in wounds would likewise have a harmful effect on the tissues. World War I and the good results obtained by Dr. Alexis Carrel¹ in the treatment of infected wounds at his hospital at Compiègne, France, brought about a widespread acceptance of wound irrigation. After experimenting with numerous disinfectants, in conjunction with Dakin, he concluded that his best results were obtained with use of a solution of sodium hypochlorite in a concentration of between 0.45 and 0.50 per cent in irrigating contaminated wounds.

Orr,² in 1925, condemned both the mechanical and the chemical method of treating contaminated wounds. It was his opinion that both were irritating to the body tissues, and he advocated, instead, immobilization of the involved part.

In 1937, Mason³ emphasized the fact that contamination is present in most wounds and stressed the importance of converting them into clean wounds. This, he believed, one could best and most easily accomplish, after first preparing

the surrounding skin, by the gentle washing of the wound with soap and water followed by irrigations with isotonic solution of sodium chloride.

Four years later, Koch⁴ stated that in his judgment there was no method so effective, and none which carried so little risk of injuring the exposed and vulnerable living tissues, as the use of plain white soap and sterile water. He advocated washing the wound gently but thoroughly for a period of not less than ten minutes with soap and water applied with soft cotton, followed by prolonged irrigation of the cleansed wound with warm isotonic solution of sodium chloride.

The wound toilet described by Whipple,⁵ which he recommended in the treatment of accidental wounds, consisted of a complete débridement followed by a thorough irrigation of the wound with isotonic saline solution. Kerrigan⁶ reported a series of 12,044 open wounds in a five year period which had been cleansed with soap and water, and he stated that his results were extremely gratifying. Estes,⁷ under the heading of "Cleansing of the Wound," recommended that the wound be washed very gently with soap and water and irrigated with isotonic saline solution.

In describing the technic used in the Cincinnati General Hospital in 1941, Stevenson⁸ condemned cleansing or irrigating the traumatic wounds. He stated that this is no substitute for thorough excision. Irrigating the wound, he believed, might spread contamination and transform a dirty wound into one that merely looks clean, and the surgeon might take liberties with it and not do a thorough débridement.

From the Department of Surgery, University of Illinois College of Medicine.

Dr. Milan Novak, of the Department of Bacteriology, assisted in these studies, and Mr. E. Hoppe gave technical assistance.

1. McDonell, W. N.: Dakin's Solution and Carrel Technic in Treatment of Infected Wounds, *U. S. Nav. M. Bull.* **12**:45-53 (Jan.) 1918.

2. Orr, H. W.: Mechanical vs. Chemical Methods in the Treatment of Wounds, *Journal-Lancet* **45**:515-518 (Nov.) 1925.

3. Mason, M. L.: The Surgical Principles Involved in the Treatment of Open Injuries, *West. J. Surg.* **45**: 239-248 (May) 1937.

4. Koch, S. L.: Primary Treatment of Wounds. *Minnesota Med.* **24**:747-749 (Sept.) 1941.

5. Whipple, A. O.: Essential Principles in Clean Wound Healing, *Surg., Gynec. & Obst.* **70**:257-260 (Feb.) 1940.

6. Kerrigan, R. L.: Exclusive Use of Soap and Water in Traumatic Wounds, *Surg., Gynec. & Obst.* **75**:163-169 (Aug.) 1942.

7. Estes, W. J.: Use of Antiseptics in Treatment of Open Wounds, *Am. J. Surg.* **47**:369-374 (Feb.) 1940.

8. Stevenson, J. M.: Surgical Care of Fresh Traumatic Wounds, *J. Missouri M. A.* **38**:378-381 (Nov.) 1941.

After studying his own results and those of other workers in the treatment of soft tissue wounds, Meleney⁹ concluded that a prolonged irrigation of the wound prior to débridement increases the incidence of infection but that a short irrigation after a dry débridement may be of value.

Ives and Hirshfeld,¹⁰ investigating the work of Hunt, found that all the clean surgical wounds that they studied were extensively contaminated with bacteria, predominantly *Staphylococcus aureus*. Jackson and Jackson¹¹ applied the work of Mason on traumatic wounds to the surgical wounds of the operating room, which Ives and Hirshfeld proved to be extensively contaminated. In a series of 200 cases, which included cases of breast amputations for carcinoma, open reductions of femur fractures and amputations at the thigh for senile gangrene, they washed the wounds with dilute green soap and water for a period of two to five minutes before closing them. They concluded that this treatment did not interfere with ideal healing of the wound but actually aided in repair, as evidenced by the absence of redness, induration and irritation.

Much has been written about the germicidal properties of soap. Walker¹² stated that pneumococci are highly susceptible to the germicidal action of soap and that streptococci are also killed by soap but that staphylococci possess more resistance to its action. In a series of experiments, Novak¹³ showed dramatically the extreme effectiveness of the germicidal activity of soap against such common bacteria as hemolytic *Staph. aureus*, *Staph. aureus* bacilli and the United States Government's standard strain for testing antiseptics (*Staphylococcus* no. 209). He found that 20 per cent green soap and 20 per cent white soap in five minutes either sterilized the cultures or reduced the number of bacteria from 25,000 per cubic centimeter to 3 or less.

Notwithstanding the fact that the germicidal property of soap is unquestionable and that the

irritative quality of soap in wounds is neither great nor particularly damaging, the superiority of cleansing with soap and water over other methods of cleansing wounds has not been definitely established. Therefore, a series of experiments on animals were devised and conducted, in the hope that information relative to this problem could be obtained.

EXPERIMENTAL METHODS

In these experiments on the prophylaxis of wound infection, both clean and contaminated wounds were studied in a series of 76 dogs. The contamination was accomplished by allowing a fixed amount of culture of hemolytic *Staph. aureus* to remain in contact with the wounds for a period of one hour prior to therapy. The relatively short duration of the bacterial contact made these wounds more closely comparable to surgical wounds produced in the operating room than to civilian or battle injuries.

All wounds were made on the carefully shaved backs of the animals, after first preparing the skin by washing with soap and water and then painting it with iodine and removing the iodine with alcohol. Pentobarbital sodium was the drug used as the anesthetic agent in all the experiments, and it was administered intraperitoneally in a solution.

1. Effect of Soap on the Healing of Noncontaminated Wounds.—The first group of dogs was used to compare the irritative qualities of 20 per cent green soap, 20 per cent white (neutral) soap and the 10 per cent green soap used for scrubbing hands in the operating rooms of the Illinois Research and Educational Hospital. Four parallel incisions were made through the skin of the dog's back, each measuring 1½ inches (3.8 cm.) in length. Hemostasis was obtained as atraumatically as possible, and each of the three incisions was soaked with one of the three soaps under investigation for a period of one hour, the fourth incision being used as a control. On application of the soaps, the wounds were covered with sterile gauze to eliminate air-borne contamination. After a period of one hour, all four incisions were carefully irrigated with isotonic solution of sodium chloride. This was done by running the sterile saline solution from a flask, suspended 3 feet (0.9 meter) above the dog, through a set used for intravenous injections. The needle was removed and the glass adapter used to direct the stream of solution into the wounds. These wounds were not scrubbed and were closed immediately after the irrigations. Interrupted mattress sutures of black silk were used and were placed in such a way that they would not enter the wound space and would give the wound good approximation without penetrating the edge. Individual collodion gauze dressings were then placed over each incision.

On the fourth and seventh days after the wounds were treated with the soaps, gross observations were made and a biopsy specimen for microscopic examination was taken from each of the wounds.

During the hour period in which the wounds of this group of dogs were being soaked with the soap solutions, the conjunctival sac and cornea of one eye was kept flooded with the 20 per cent green soap and the other flooded with the 20 per cent white soap. The eyes were observed for inflammation and keratitis after one hour, after twenty-four hours and on the fourth day.

9. Meleney, F. L.: A Statistical Analysis of a Study of the Prevention of Infection in Soft Part Wounds, Compound Fractures, and Burns with Special Reference to the Sulfonamides, *Surg., Gynec. & Obst.* 80:263-296 (March) 1945.

10. Ives, H. R., Jr., and Hirshfeld, J. W.: Bacterial Flora of Clean Surgical Wounds, *Ann. Surg.* 107:607-617 (April) 1938.

11. Jackson, R. H., and Jackson, R. H., Jr.: A Simple, Efficient Method to Diminish the Incidence of Primary and Secondary Infection in Surgical Wounds, *Surgery* 6:398-409 (Sept.) 1939.

12. Walker, J. E.: The Germicidal Properties of Chemically Pure Soaps, *J. Infect. Dis.* 35:557-566 (Dec.) 1924.

13. Novak, M. V.: Personal communication to the author.

2. *Effect of Scrubbing on the Healing of Noncontaminated Wounds.*—To compare the irritation of soap and mechanical scrubbing with the irritation of the soap alone, three of incisions of the same type were made on the back of each dog. The first was washed gently with cotton and white soap for a period of ten minutes; the second, with surgical gauze dressings and white soap for the same length of time, and the third wound was prepared to be used as a control by just soaking it with the same soap for the same length of time. After ten minutes all three wounds were irrigated with isotonic solution of sodium chloride and sutured and dressed in the manner previously described. On the fourth day, the wounds were observed grossly, materials for cultures taken and the biopsy specimens taken for microscopic examination.

3. *Effect of Soap and Scrubbing on the Healing of Contaminated Wounds.*—To the wounds of the next group of dogs was added bacterial contamination. Six incisions were made on the back of each of these dogs and contaminated with 0.1 cc. of a twenty-four hour culture of hemolytic *Staph. aureus*. This culture contained approximately 1,100,000,000 bacteria per cubic centimeter. After the bacteria had been in the wounds for a period of one-half hour, the first wound was filled with 20 per cent green soap, the second was filled with 20 per cent white soap and the third was washed gently with a cotton applicator and white soap for a period of sixty seconds. A gauze-tipped forceps and white soap were used to wash out the fourth wound. The fifth and sixth wounds were not treated with soap. After a period of one hour, each wound except the sixth (which was used as a control wound) was irrigated thoroughly with 250 cc. of isotonic solution of sodium chloride. All wounds were then closed and observed and materials taken for cultures on the fourth postoperative day.

4. *Effect of Irrigation with Various Quantities of Isotonic Solution of Sodium Chloride on the Healing of Contaminated Wounds.*—On the back of each of the last group of dogs, four transverse incisions were made, and, after proper hemostasis, were contaminated as described previously. After a period of one hour, the first wound was irrigated with 1,000 cc. of isotonic solution of sodium chloride in the manner previously described; the second was irrigated with 500 cc. of solution, and the third, with 250 cc. of solution. The last wound was used as a control and not irrigated. The four incisions were then closed, and an individual collodion gauze dressing was placed on each. After four days, the wounds were observed and materials for cultures taken.

The technic of the bacterial examination of the wounds was as follows: After removal of the collodion gauze with the aid of ether, the incisions were painted with tincture of iodine solution. A sterile capillary Wright pipet was placed into the wound, and fluid, if present, was drawn up the tube for a distance of 1 cm. The fluid obtained in this way was then emptied into a sterile tube containing 5 cc. of warm sterile agar and then emptied into a sterile Petri dish and incubated at 37 C. for twenty-four hours. After this length of time, the number of colonies growing in each Petri dish was counted and recorded.

RESULTS OF THE EXPERIMENTS

1. *Effect of Soap on the Healing of Noncontaminated Wounds.*—As previously stated, all the wounds soaked with the 20 per cent green

soap, 20 per cent white soap and 10 per cent green soap for a period of one hour and the control wounds, with no soap, were irrigated with isotonic solution of sodium chloride and then closed. Eleven dogs were used in this experiment. Most of the wounds in this group healed per primam. No difference in the amount of infection could be determined by gross examination or bacteriologic study. However, microscopically there was slightly less inflammatory cell infiltration and slightly more fibroplasia between the wound edges in the biopsy specimens taken from the control wounds. No difference could be detected microscopically between the wounds treated with 20 per cent green soap and 20 per cent white soap, but these wounds showed more inflammatory response and less fibroplasia than the wounds treated with the 10 per cent green soap.

The eyes of the dogs in this group had been flooded with soap for a period of one hour—20 per cent green soap in the left eyes and 20 per cent white soap in the right eyes. In the eyes of all the dogs, definite signs of irritation were present. The white soap formed a pseudomembrane over the cornea; however, after the eyes were washed with isotonic saline solution, the underlying signs of inflammation were approximately the same in the two eyes of each dog. The conjunctival vessels were engorged to approximately three times normal size. The corneas lost their luster, and an obvious keratitis was present one hour after the soap had been removed. This was evidenced by the whitening of the corneas, which was still present on observation on the fourth day, and no difference could be discerned between the actions of the two soaps.

2. *Effect of Scrubbing on the Healing of Noncontaminated Wounds.*—In the second experiment 6 dogs were used, and three incisions were made on the back of each dog. The first incision was washed with gauze and white soap; the second, with cotton and white soap, and the third, which was the control wound, was merely soaked with white soap for a period of ten minutes. These wounds were then irrigated with isotonic solution of sodium chloride and closed. There was a decided and consistent difference microscopically. This difference did not show grossly, for all wounds healed without gross evidence of inflammation. On the fourth postoperative day, the wounds washed with gauze exhibited microscopically the greatest amount of inflammatory cell infiltration of the wound edges and the least fibroplasia. The control wounds, which were not washed mechanically but just bathed in the soap, showed little or no inflammation microscopically.

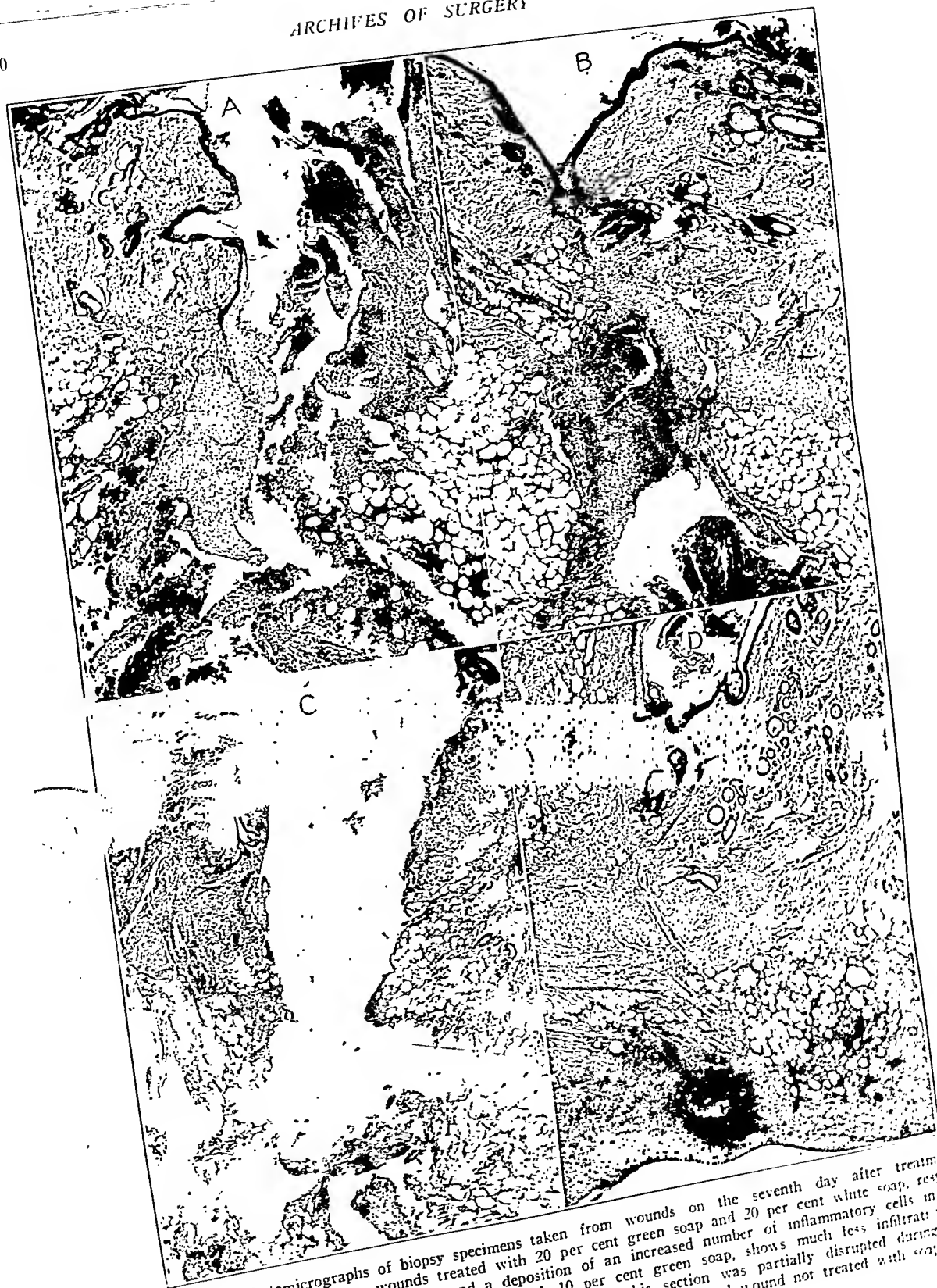


Fig. 1.—Photomicrographs of biopsy specimens taken from wounds on the seventh day after treatment. Sections A and B are from wounds treated with 20 per cent green soap and 20 per cent white soap, respectively. Both show delayed fibroplasia and a deposition of an increased number of inflammatory cells in the area. Section C, taken from a wound healing, shows much less infiltration of leukocytes but little tendency toward section. Section D represents the control wound not treated with soap and shows good healing and little evidence of inflammation.

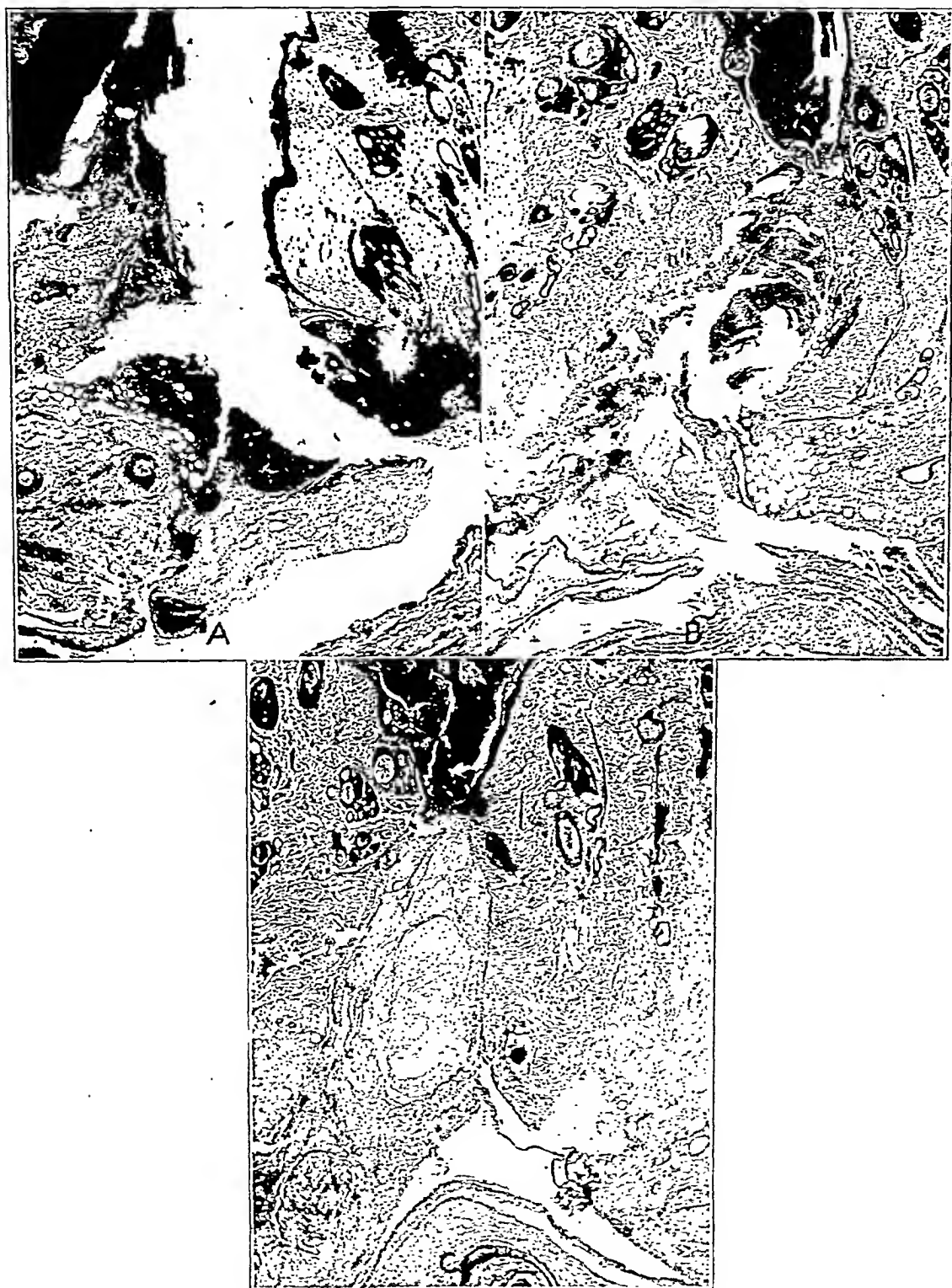


Fig. 2.—Photomicrographs of biopsy specimens taken from wounds on the fourth day after treatment. Section *A*, taken from a wound scrubbed with gauze and white soap for ten minutes, shows little evidence of fibroblastic proliferation and a large amount of inflammatory cell infiltration. Section *B*, taken from a wound scrubbed with cotton and white soap, shows less infiltration of leukocytes and many fibroblasts connecting the wound edges. The control wound, section *C*, shows a solid union of the wound edges with practically no microscopic evidence of inflammation.

and a solid union of the wound edges with fibroblasts. The wounds washed with cotton and soap for the ten minute period took the middle point microscopically, both in healing and in the inflammatory changes around the wound edges.

3. *Effect of Soap and Scrubbing on the Healing of Contaminated Wounds.*—The third series of experiments, performed on 48 dogs, added the effect of *Staph. aureus* contamination to the other factors already included in the previous experiments. The bacteria were left in contact with the wounds for half an hour. Twenty per cent green soap was added to the first incision and 20 per cent white soap to the second incision for a period of one-half hour. The third and fourth wounds were mechanically scrubbed with gauze and white soap, and cotton and white soap, respectively, for sixty seconds. Each of the first five incisions was then irrigated with 250 cc. of isotonic solution of sodium chloride, and the sixth wound was not treated.

TABLE 1.—*Comparison of Various Methods of Cleansing Wounds Contaminated with Hemolytic Staphylococcus Aureus*

Type of Cleansing	Average Degree of Infection*
Wounds soaked with green soap for one-half hour....	2.69
Wounds soaked with white soap for one-half hour....	2.14
Wounds washed with gauze and white soap for sixty seconds	1.69
Wounds washed with cotton and white soap for sixty seconds	1.54
control wounds—not treated with soap or irrigation	1.43
wounds irrigated with isotonic saline solution only...	0.38

* 0 indicates that the wound healed per primam with no infection. Infections were graded from 1 to 4, 4 representing the most severe grade.

In the analysis of results of the experiments in this series, cultures were practically useless. When any fluid was obtained from a wound, the culture yielded an innumerable quantity of colonies. When no fluid was found in a wound, the culture yielded from no colonies to six colonies.

The resultant effects of the bacteria in the various wounds treated in the described manner were, therefore, determined by the degree of infection produced. This was related particularly to the amount and type of exudate observed. The degree of infection in the wounds was arbitrarily graded from 0 to 4. When the wound appeared to have healed per primam with no collection of fluid, it was graded 0, and the wounds were graded from 1 to 4 depending on the degree of infection. This was determined by the amount of purulent fluid present in the wound and the extent of induration, redness, heat, lack of healing, etc. Table 1 summarizes the results of this experiment.

The contaminated wounds treated with white soap and green soap for one-half hour, as previously described, exhibited at the end of the fourth day greater amounts of infection than those treated in other ways. In all these wounds, large abscesses formed. However, in the wounds which had been soaked in green soap before closure, the most infection consistently developed, the average grades being 2.69 for the wounds soaked with green soap and 2.14 for the wounds soaked with white soap.

The majority of the wounds washed with gauze or cotton and soap for sixty seconds before irrigation became infected, but the degree of inflammation was less in these than in the wounds soaked with green and with white soap for one-half hour. The average grade given the wounds cleansed with gauze and white soap was 1.66. When cotton was substituted for gauze, the average was 1.54.

After computation of an average of the degree of infection in the various types of wounds, it was revealed that the least infection was present in the wounds that were not treated with soap but were only irrigated with isotonic solution of sodium chloride; this figure was 0.38, representing a minimal amount of infection.

The degree of infection of the wounds contaminated by bacteria but not subjected to any local form of treatment averaged 1.43, which compares unfavorably with that of the wounds which were contaminated and then irrigated with isotonic saline solution.

4. *Effect of Irrigation with Various Quantities of Isotonic Solution of Sodium Chloride on the Healing of Contaminated Wounds.*—When it was discovered that the wounds irrigated with isotonic saline solution healed better than any of the other wounds, including the controls, it was decided to attempt to find out whether there is an optimum amount of irrigation from the standpoint of wound healing. Accordingly, in a group of 11 dogs, four incisions were made on the prepared back of each dog, and each wound was contaminated with the standard amount of the culture of hemolytic *Staph. aureus*. After a period of one hour, the first wound was irrigated with 1,000 cc. of isotonic solution of sodium chloride; the second, with 500 cc. of the solution, and the third wound was irrigated with just 250 cc. of the solution. The fourth wound, which was used as a control, was not irrigated. All wounds were closed and were observed and cultures taken after four days. The wounds in this experiment were graded from 0 to 4 on each of six points, namely (1) the amount of exudate outside the wound, (2) the amount of fluid within the wound, (3)

the amount of induration of the wound, (4) the degree of wound healing, (5) the presence of stitch abscesses and (6) the amount of redness of the wound. Again, the cultures were of no value in grading the wounds; the majority of the cultures showed innumerable colonies of bacteria. The result of this experiment is summarized in table 2.

TABLE 2.—Comparison of Wounds Contaminated with Hemolytic *Staphylococcus Aureus* and Cleansed with Irrigations of Various Quantities of Isotonic Solution of Sodium Chloride

	Control Grade	Amount of Solution		
		250 Cc. Grade	500 Cc. Grade	1,000 Cc. Grade
Exudate.....	1.72	1.45	0.65	0.72
Fluid within wound.....	1.45	0.64	0.33	0.26
Induration.....	1.91	0.91	0.66	0.72
Lack of healing.....	1.57	0.56	1.00	0.57
Stitch abscesses.....	1.45	1.15	1.33	1.00
Redness.....	0.15	0	0	0
Average *.....	1.35	1.00	0.79	0.67

* The wounds were graded from 0 to 4, as in table 1. Zero represents no evidence of the characteristic indicated. Maximum evidence was graded as 4.

The control wounds in this experiment, which were contaminated with bacteria but not irrigated with isotonic saline solution, were the wounds most infected. Though the wounds irrigated with 250 cc. of solution were definitely less infected than the controls, the wounds irrigated with 500 cc. of solution were even less infected, and the least infected wounds were the ones irrigated with 1,000 cc. of isotonic saline solution.

SUMMARY

There is no doubt as to the efficacy of the various soaps as germicidal agents. However, in these experiments, when the soaps were placed in actual contact with the uncontaminated fresh wounds, they produced a definite but slight irritation. This was noted only on microscopic examination; gross examination revealed no difference between control wounds and wounds into which soap had been placed. However, in wounds which were contaminated by placing a given amount of a culture of *Staph. aureus* within their depths and then exposed to soap, there was a definite increase in signs of infection over those found in the control wounds not exposed to soap; "green" soap was found more irritating than "white" soap.

The harmful effect of mechanical washing of the wounds is in direct proportion to the coarseness of the material used.

These experiments indicated that of the various methods studied the cleansing of contaminated wounds by a gentle irrigation with isotonic solution of sodium chloride is the most effective prophylaxis of wound infection. Contaminated wounds treated by this gentle irrigation healed with less evidence of infection than did control contaminated wounds subjected to no treatment other than closure at the specified time. Best results in cleansing these small wounds were obtained by irrigating them with 1,000 cc. of saline solution with no scrubbing, utilizing the force of the stream as the washing mechanism.

OSSEOUS, CARTILAGINOUS AND MIXED TUMORS OF THE HUMAN BREAST

A REVIEW OF THE LITERATURE

ANTONIO ROTTINO, M.D., AND KATHLEEN WILLSON

NEW YORK

During the past century an interesting literature pertaining to a group of rare tumors of the breast has developed. Collectively they are characterized by the presence of bone, cartilage, fibrous tissue and pleomorphic cells; and, depending on whether these elements are found alone or in combination, the tumors have been reported as chondroma, osteochondroma, chondrosarcoma, osteochondrosarcoma, osteosarcoma, osteoid sarcoma, giant cell sarcoma, myeloid sarcoma, mixed tumor, osteoclastoma and teratoma.

In 1700 Bonet¹ reported observing in a female breast a stony hard mass "which could not be cut with a knife." Since at this period microscopic study of tissue had not evolved and also because stony hard tumors were called bony or cartilaginous, it would be inaccurate to refer to this early contribution as the first example of the tumors under discussion. The same critical attitude must be maintained toward the bony and cartilaginous tumors reported by Morgagni,² Reil,³ Cooper,⁴ Warren,⁵ Cruveilhier⁶ and Velpeau.⁷ As Foucher's⁸ enchondroma arose from costal cartilages and not from mammary gland, his contribution must also be discarded. The first case of this group to be reported with microscopic study came from the pen of Lancereaux⁹ in 1860. Subsequently, tumors from about 105 other cases were described. We have studied all but 8¹⁰ of these reports and feel that it would not be amiss to present an analysis of them.

ENCHONDROMA

Seven cases of enchondroma constitute this group, in all of which the tumors occurred in females from 14 to 54 years of age. The patients were cognizant of their tumors from one to thirty-two years. The tumors grew slowly and progressively in 5 patients and after a long stationary period in 1. Mastectomy was performed in 1 case, and in the remaining cases the treatment was excision. The postoperative course in all instances proved uneventful. Six months after operation a recurring tumor was removed in Cambria's case. As to the observations on physical examination, a palpable mass was observed to occupy any portion of either breast (the left in 4 cases, and the right in 2). These masses were well circumscribed, round, hard and freely movable and ranged in size "from that of a cherry to that of a fist." A few only were described as having a capsule.¹¹ The tumor appeared, as a rule, gray and, for the most part, solid. In 1 case a cyst was present,^{11b} and in others¹² there were areas of calcification. The microscopic components consisted of hyaline cartilage and fibrocartilage, fibrous tissue and cartilage cells. The amounts of each varied in different cases. In some cases the fibrous tissue was rich in fibroblasts. Glandular elements were present in the tumor described by Davidsohn.

One would assume from the length of their duration that the tumors were benign. Yet in 1 instance a tumor present eighteen years recurred six months after excision. The author described nothing in the clinical history of the patient or in the pathologic condition of the tumor to indicate malignancy, unless one considers it significant that after fourteen years of quiescence the

From St. Vincent's Hospital.

1. Bonet, T.: *Sepulchretum, sive anatomia practica ex cadaveribus, morbo denatis*, Geneva, Cramer et Perachon, 1700, book 3, chap. 61, p. 522.

2. Morgagni, J. B.: *De sedibus et causis morborum*, Ebroduni in Helvetia, 1779, vol. 3, epistol. 50, obs. 41 and 43, p. 42.

3. Reil: *Arch. f. d. Physiol.* 3:437, 1799.

4. Cooper, A. P.: *Illustrations of the Diseases of the Breast*, London, Longman, Rees & Co., 1829, p. 65.

5. Warren, J. C.: *Surgical Observations on Tumours*, Boston, Crocker & Brewster, 1837, p. 213.

6. Cruveilhier, J.: *Traité d'anatomie pathologique générale*, Paris, J.-B. Baillière & fils, 1856, vol. 3, p. 824.

7. Velpeau, A.: *Traité des maladies du sein et de la région mammaire*, Paris, V. Masson, 1854.

8. Foucher: *Union méd.*, Paris 3:403, 1859.

9. Robin and Lancereaux, E.: *Bull. Soc. anat. de Paris* 35:293, 1860.

10. Reports of cases by the following authors cited by Raso^{10b} were not available to us: Monoki, Salarron, Guizzetti, DuBar, Molin, Soulier, DeSeil and Parreira.

11. (a) Amann, J. J.: *Beitr. z. Geburtsh. u. Gynäk.* 4:57, 1869. (b) Pied: *Bull. Soc. méd. de l'Yonne* (1879) 20:50, 1880. (c) Stefani, D.: *Gaz. d. med.* 9:564, 1888. (d) Rey: *Lyon méd.* 100:259, 1903.

12. Borst, M.: *Geschwulstlehre* 2:661, 1902. Ann.^{11a}

tumor renewed its growth and increased from "acorn to pullet egg size." Significantly, the recurrence was composed of hyaline cartilage, indicating its true neoplastic potentialities.

Facts worth noting are that no case of enchondroma of the human breast has been reported since 1909 and that there are no data on the

in females from 12 to 89 years of age. Most patients were aware of the growth for a long time, nine to forty-nine years. In addition to consciousness of a mass, 2 patients experienced pain.¹³ In 1 of these this did not happen, until the tumor ulcerated through the skin and became infected. In those cases in which the tumor

TABLE 1.—*Enchondroma*

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptoms	Treatment	Follow-Up
1. Amann: Beitr. z. Geburtsh. u. Gynäk. 4: 57, 1860	1860	54	32 yr.	Growing mass; pain	Shelling out	None
2. Pied: Bull. Soc. méd. de l'Yonne (1879) 20: 50, 1880	1879	14	1 yr.	Large left breast	Excision	None
3. Cambria: Riv. ven. di sc. med. 6: 340, 1887	1887	19	15 yr.	Mass	Excision	Recurrence in 6 months
4. Stefanini: Gaz. d. osp. 9: 564, 1888.....	1888	59	25 yr.	Mass; pain	Excision	None
5. Borst: Geschwulstlehre 2: 681, 1902.....	1902	No history
6. Rey: Lyon méd. 100: 259, 1903.....	1903	25	6 yr.	Mass	Mastectomy	None
7. Davidsohn: Zentralbl. f. Gynäk. 33: 1357, 1909	1909	51	?	Mass	Shelling out	None

TABLE 2.—*Chondrosarcoma*

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptoms	Treatment	Follow-Up
Coats: Glasgow M. J. 4: 45, 1871.....	1871	..	No history
Bowly: Tr. Path. Soc. London 35: 306, 1882..	1882	42	1 yr.	Mass	Mastectomy	Recurrence in 6 mo.; death; autopsy
Clarke: Tr. Path. Soc. London 41: 229, 1891..	1890	46	2-3 yr.	Mass	Mastectomy	None
Poulsen: Arch. f. klin. Chir. 42: 638, 1891.....	1891	Mass	Excision	Recurrence 6 and 12 mo.; death 1 yr. later
Horner: Beitr. z. klin. Chir. 12: 619, 1894.....	1894	59	49 yr.	Ulcerated mass; pain	Mastectomy	Well after 4 yr.
Happel: Beitr. z. klin. Chir. 14: 721, 1895.....	1895	33	10 yr.	Mass	Excision	None
Wacker, cited by Happel						
Holder: Memphis M. J. 16: 66, 1896.....	1896	12	9 mo.	Mass	Excision	None
Morton: Tr. Path. Soc. London 54: 327, 1904..	1904	64	1 mo.	Mass	Mastectomy; axilla cleared	Several recurrences within 15 mo.; death shortly afterward
Gullbaud: Gaz. méd. de Nantes 24: 372, 1906..	1906	?	13 yr.	Mass	Excision	None
Leclère: Rev. de chir., Paris 33: 434, 1906.....	1906	25	?	Mass	Enucleation	None
Watson: Catalogue of the Museum of the Royal College of Surgeons, 1909	1909	60	2 mo.	Mass	?	Recurrence in 3 mo.
Orlando: Osp. maggiore 1: 519, 1913.....	1913	..	No history
Kaufmann: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 3, p. 1785	1922	57	27 yr.	Mass	?
Thiemes: Virchows Arch. f. path. Anat. 264: 150, 1927	1926	43	5-6 mo.	Mass	Mastectomy	None
D'Aunoy and Wright: Ann. Surg. 92: 1059, 1930	1930	46	9 yr.	Mass	Mastectomy	None
Wakeley: Brit. J. Surg. 21: 156, 1933.....	1933	89	?	Mass	Mastectomy	Well after 1 yr.
Berner: Ztschr. f. Krebsforsch. 46: 232, 1937...	1937	63	?	Mass	Mastectomy	Recurrence in 9 mo.; died at 10 mo.; autopsy
Sallor (case 3): Am. J. Cancer 31: 183, 1937...	1937	65	4 yr.	Mass	Biopsy	Died in 5 mo.
Anzilotti: Arch. ital. di med., Sperimentale 3: 513, 1938	1938	36	1 mo.	Mass; pain	?	None
Allen: Arch. Path. 29: 589 (May) 1940.....	1940	28	2½ yr.	Mass	Radical

ultimate outcome in the ones reported prior to that year. It would appear advisable, therefore, for future contributors to allow a sufficiently long period to elapse before publishing reports.

CHONDROSARCOMA

Twenty-one reports of malignant cartilaginous tumors of the breast were found, all occurring

was present many years the rate of growth was usually slow at first and rapid later. In 1 instance it was continuously slow until the tumor achieved conspicuous size. In still another the growth enlarged only during periods of pregnancy. The most rapidly growing tumors were

13. (a) Horner, F.: Beitr. z. klin. Chir. 12: 619, 1894. (b) Anzilotti, G.: Arch. ital. di med., Sperimentale 3: 513, 1938.

those discovered one to nine months before medical consultation.

In regard to physical observations, either breast was likely to be involved. The growths as a rule were freely movable. Only one became adherent to the skin, and this one ulcerated.

The patients were treated either by simple mastectomy or by excision. In 1 instance a radical operation¹⁴ was done. Of the 6 patients for whom there were follow-up data, 2 were living one and four years after operation. The remaining 4 suffered recurrence in six to twelve months and were dead in one to two years. The prognosis is thus essentially poor.

The tumors varied from "pigeon egg, goose egg, apple size, to twenty centimeters" in diameter. In general they were irregular, round and sharply demarcated, and some were encapsulated.¹⁵ Their color was given as gray-white and their consistency as dense, firm and hard.

In the case of Berner autopsy disclosed metastases to the chest wall, pleura and lungs, as well as recurrences in the skin about the operative scar. The pulmonary metastases were nodular and varied in size and distribution through the two lungs. Microscopic examination of the pulmonary tumors, of the mass in the wall of the chest and of the cutaneous recurrences showed a picture similar to that of the original tumor, namely, of cartilaginous composition and richness in giant cells. In Morton's case the gluteal metastasis was found to contain many round cells and cartilage undergoing calcification. In the breast the cells were of the spindle type.

OSTEOCHONDROMA

Eight cases of osteochondroma comprise this group. The essential available clinical data are summarized in table 3. Thereto the following supplemental facts should be added, namely that

TABLE 3.—*Osteochondroma*

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptoms	Treatment	Follow-Up
Durham: Brit. M. J. 2:1019, 1883.....	1883	23	No history	No history	Excision
Battle: Tr. Path. Soc. London 37:473, 1886...	1886	73	5 yr.	Mass	Mastectomy	No recurrence in 9 mo.
Leser: Beitr. z. path. Anat. u. Physiol. 11:382, 1887	1888	67	16 yr.	Mass	Excision	None
Sehrt: Beitr. z. klin. Chir. 55:589, 1907.....	1907	44	6 mo.	Mass	Mastectomy; axilla cleared	None
Chevrier and Delval: Bull. et mém. Soc. anat. de Paris 85:588, 1910	1910	56	2 mo.	Mass	?	None
Fowler: Northwest Med. 24:122, 1925.....	1925	67	10 mo.	Mass; pain	Radical	None
Re: Brit. J. Surg. 14:323, 1926.....	1927	50	9 mo.	Mass	Mastectomy	None
Äki: Deutsche Ztschr. f. Chir. 219:413, 1929..	1929	76	6 mo.	Mass	Excision	None

While some tumors presented a uniform appearance, others were in part hard and in part composed of solid soft tissue. Several were cystic. Three tumors contained areas of calcification.

All the tumors contained cartilage in varying amounts and variously distributed through a fibrous or cellular stroma. The cells were of diverse types, being spindle, round, oval or polymorphous. Three tumors¹⁶ contained large multinuclear giant cells. Lecène described the cells in the case reported by him as of the "epulis" type. The stroma in a few cases appeared myxomatous.¹⁷ In 3 cases remnants of glandular tubules were found in the tumor.

14. Morton, C. A.: Tr. Path. Soc. London 54:327, 1904.

15. Lecène, P.: Rev. de chir., Paris 33:434, 1906. Anzilotti.^{12b}

16. Berner, O.: Ztschr. f. Krebsforsch. 46:232, 1937. Footnote 15.

17. (a) Poulsen, K.: Arch. f. klin. Chir. 42:638, 1891, (b) Holder, A. B.: Memphis M. J. 16:66, 1896. (c) Allen, A. C.: So-Called Mixed Tumors of Mammary Gland of Dog and Man, with Special Reference to

the tumors as a group were of slow growth, continuous in some cases and periodic in others; that only 1 patient suffered pain, and that the physical examination revealed a firm, freely movable, nontender mass, the overlying skin of which was smooth and uninvolved.

Grossly the tumors were hard and lobulated and varied from a few millimeters to 10 cm. in diameter. All were well demarcated, and four were encapsulated. While three specimens were cystic, five others were solid and composed largely of gray tissue in which, in some cases, bone and cartilage were grossly detectable.

Microscopically the tumors were composed of fibrous tissue, cartilage and spongy bone. In 1 case there was also osteoid tissue. Spindle, round and multinuclear giant cells constituted the cellular components of the tumors. The amounts of these elements varied from case to case. In 3 instances glands were found in the tumor. In Fowler's case calcification was shown.

General Problem of Cartilage and Bone Formation. Arch. Path. 29:589 (May) 1943. Anzilotti.

OSTEOCHONDROSARCOMA

In most of the cases in this group osteochondrosarcoma occurred in persons who were in the sixth decade and all of whom were older than 40 years. In contrast to the persons whose cases are summarized in the previous tables (who had growths for many years), the majority of those with growths of this type came under medical observation comparatively early. Their tumors varied in size and in rate of growth. In a case in which the neoplasm was neglected it attained the dimensions of a man's head, became fixed to the skin and ulcerated.

Arnold's patient noted a gradual enlargement of the breast. The surmise that there was an abscess led to the making of an incision. Since

morphous in character. Large and multi-nucleated giant cells were noted in 7 cases. Bauer described as many as three hundred nuclei in the giant cells of his patient. The tumor in Kurosu's patient simulated an epulis growth. Two of the neoplasms were in part fibroadenoma.¹⁹

A word must be said concerning the nature of the recurrent tumors and the metastases in those cases in which autopsies were performed. The pulmonary metastases in Stilling's case contained osteoid tissue, cartilage and cellular elements. Two separate and distinct nodules were removed from Le Riche and Cavaillon's patient. One was carcinoma; the other, sarcoma containing cartilage and bone. At autopsy recurrent growths were found in the axilla and wall

TABLE 4.—*Osteochondrosarcoma*

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptoms	Treatment	Follow-Up
Heurtaux: Bull. et mém. Soc. de chir. de Paris 1:94, 1875	1874	52	6 mo.	Mass; pain	Mastectomy	Recurrence in 6 mo.; death; no autopsy
Stilling (case 2): Deutsche Ztschr. f. Chir. 15: 247, 1881	1881	53	1½ yr.	Mass	Excision	Died following operation; metastasis to lung
Arnold: Virchows Arch. f. path. Anat. 148: 449, 1897	1897	67	6 mo.	Mastectomy; axilla cleared	None
Le Riche and Cavaillon: Bull. et mém. Soc. anat. de Paris 83:400, 1905	1905	40	?	Mass	Mastectomy	Recurred; death in 2 mo.
Kaufmann: Pathology for Students and Practitioners, translated by S. P. Reimann, Philadelphia, P. Blakiston's Son & Co., 1929	1922	52	No history	No history
Kurosu: Ztschr. f. Krebsforsch. 26:99, 1927....	1927	80	6 mo.	Mass	Mastectomy	Death in 1 yr.; no information
Busser: Ann. d'anat. path. 5:340, 1928; G: 1247, 1929	1929	50	?	Mass	Mastectomy; axilla cleared	Recurrence in 1 yr.
Banet: Bull. Liga contra el cáncer 8:321, 1933	1933	57	2 yr.	Mass	Radical; roentgen	Well at 5 mo.
Sailor (case 4): Am. J. Cancer 31:183, 1937....	1937	59	6 wk.	Mass	Mastectomy	Well at 2 yr.
Raso: Pathologica 29:229, 1937.....	1937	45	2 mo.	Mass	Radical	10 mo. metastasis to lung; no autopsy
Sullivan: Illinois M. J. 82:140, 1942.....	1942	43	2 mo.	Mass	Excision	None
Freshman: Rocky Mountain M. J. 37:981, 1940	1942	52	3 yr.	Mass	Radical	Well at 10 yr.

healing did not follow, the breast was removed. In Sailor's case growth was rapid; in the remaining cases no note was made of the rapidity of growth. In 3 cases the tumor proved definitely malignant; in 2 the patients remained well two to ten years after operation. No follow-up information was given in the remaining 5 cases.

The largest tumor measured 16 cm.; another, 8 by 10 cm.; the smallest was the size of a pigeon's egg. A few were freely movable and not fixed to surrounding structures. One tumor was described as sharply demarcated. Most were solid. Cysts were present in 3 cases.¹⁸

Microscopic examination revealed bone and cartilage in all the tumors. All were richly cellular, the cells being round, spindle and poly-

of the chest. These consisted of "complex cartilage." There were no generalized metastases. Busser first considered the tumor in his patient to be an adenofibroma exhibiting metaplasia of bone and cartilage. In the recurrence he noted cartilage, osteoid tissue, osteoblasts, numerous giant cells and areas of fibrosarcoma. The last was not seen in the original tumor. Removed from the thigh of Raso's patient was a metastatic growth containing bone and cartilage as well as cellular elements. Bone was not noted in the primary growth.

OSTEOSARCOMA

As can be seen from table 5, "ossifying sarcoma" of the breast accounts for a small group of cases. In Schreiner's case the tumor was stationary for thirty-nine years, after which it

18. Arnold, S. K.: Virchows Arch. f. path. Anat. 148:449, 1897. Sullivan, S. J.: Illinois M. J. 82:140, 1942. Freshman, A. W., and Kurland, S.: Rocky Mountain M. J. 37:981, 1940.

19. (a) Busser, F.: Ann. d'anat. path. 5:340, 1928. (b) Raso, M.: Pathologica 29:229, 1937.

grew rapidly. This patient died from intra-thoracic metastasis one year after operation. The only clinical symptom in the entire group was a sense of mass.

Gross descriptions are meager. In general the tumors were globular, hard and cystic. All

contained bone. In Sutton's case the microscopic picture was so similar to that of osteogenic sarcoma of bone that the patient was submitted to careful examination for a primary osseous tumor. Beckton noted the presence of considerable fibrous tissue and areas rich in cells, par

TABLE 5.—*Osteosarcoma*

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptom	Treatment	Follow-Up
Stilling (case 1): Deutsche Ztschr. f. Chir. 15: 247, 1881	1881	56	6 mo.	Mass	Excision	Died 2 years later; no autopsy
Sutton: Arch. Middlesex Hosp. 19: 98, 1910...	1910	73	2 mo.	Mass	Mastectomy; axilla cleared	None
Beckton: Arch. Middlesex Hosp. 27: 215, 1912	1912	52	5 mo.	Mass	Mastectomy; axilla cleared	None
Schreiner and Thibaudenu: Ann. Surg. 95: 433, 1932	1932	57	40 yr.	Mass	Excision; later mastectomy; postoperative roentgen therapy	Thoracic metastasis; died in 1 year; no autopsy
Gomori: Am. J. Surg. 33: 150, 1936.....	1936	64	6 mo.	Mass	Mastectomy	None

TABLE 6.—*Osteoid Sarcoma; Giant Cell Sarcoma*

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptoms	Treatment	Follow-Up
Lancereaux: Bull. Soc. anat. de Paris 35: 293, 1890	1890	46	6 mo.	Slow-growing tumor which ulcerated; lancinating pain	Excision	Follow-up period too short
Haward: Tr. Clin. Soc. London 7: 106, 1874....	1874	64	13 yr.	Recurring tumor	Excision; then mastectomy	Involvement of chest wall; death; autopsy
Stilling (case 3): Deutsche Ztschr. f. Chir. 15: 247, 1881	1881	59	10 yr.	Mass; pain	Mastectomy	Nine recurrences; death; autopsy
Pillier: Bull. et mém. Soc. anat. de Paris 4: 552, 1890	1890	No history				
Noetzel: Ein Beitrag zur Kenntnis der Fibroadenome der weiblichen Brustdrüse, Berlin, G. Schade, 1892	1891	No history				
Snow: Tr. Path. Soc. London 46: 184, 1895....	1895	62	No further history	Radical	Recurrence
Manz: Beitr. z. klin. Chir. 13: 66, 1893.....	1895	52	3 mo.	Rapidly growing mass	Mastectomy	Recurrence in 5 mo.; death in 1 year with metastasis to lung
Heuter and Karrenstein: Virchows Arch. f. path. Anat. 183: 493, 1906	1906	37	12 yr.	Mass, stationary for 11 years	None	Death shortly after admission to hospital
Lorrain and Ménard: Bull. et mém. Soc. anat. de Paris 84: 103, 1909	1909	56 Male	1 yr.	Rapidly growing mass	None	No follow-up
Desmarest and Masson: Bull. et mém. Soc. anat. de Paris 87: 251, 1912	1912	52	12 yr.	Mass	Radical	
Orlando: Osp. maggiore 1: 519, 1913.....	1913	No history			Mastectomy	Death in 2 mo.
Moure and de Jong: Bull. et mém. Soc. anat. de Paris 89: 32, 1914	1914	67	2 yr.	Mass	Mastectomy	Axillary nodes involved
Jessup: Proc. New York Path. Soc. 19: 117, 1919	1919	..	6 mo.	Mass	Radical	Death in 10 mo., probably from metastasis to liver; no autopsy
Fry: J. Path. & Bact. 30: 528, 1927.....	1927	55	5 mo.	Mass		None
Edelmann: Beitr. z. path. Anat. u. z. allg. Path. 78: 618, 1927	1927	51	Mass	Excision	Recurrence in 7 mo.
Wellbrock: Ann. Surg. 90: 154, 1929.....	1929	57	2 mo.	Mass	Mastectomy	Death in 2 yr.
Calignris: Cancro 3: 226, 1933.....	1932	61	6 mo.	Mass	Radical	Death in 1 yr.; diagnosis; no autopsy
Hartmann and others (case 1): Bull. Assoc. franç. p. l'étude du cancer 22: 378, 1933	1933	27	19 yr.	Mass	Excision; radical	Death in 7 1/2 years; apparently from metastasis
Hartmann and others (case 2): Bull. Assoc. franç. p. l'étude du cancer 22: 378, 1933	60	30 yr.	Mass	Excised	Recurrence in 1 yr.; death in 2 mo.; metastasis to liver
Hartmann and others (case 3): Bull. Assoc. franç. p. l'étude du cancer 22: 378, 1933	3 wk	Mass	Excision; radium	Death in 1 yr.; apparently from metastasis
Rose: Deutsche Ztschr. f. Chir. 240: 151, 1936	1935	26	10 yr.	Mass		Death in 6 mo.; no autopsy
Guérin: Bull. Assoc. franç. p. l'étude du cancer 25: 326, 1936	1936	65	1 mo.	Mass	Radical; carcinoma also present	Postoperative metastasis; death in 17 mo.
Di Steffano: Tumori 23: 482, 1937.....	1937	50	Mass		Recurrence; death in 1 mo.; death from pulmonary embolism
Holm (case 1): Acta path. et microbiol. Scand. 17: 506, 1940	1940	50	50 yr.	Mass	Excised	Death in 6 weeks
Holm (case 2): Acta path. et microbiol. Scand. 17: 506, 1940	62	2 mo.	Mass	Mastectomy	

ticularly giant cells having as many as sixty nuclei. The histologic picture in Schreiner's case was essentially similar, except that some of the connective tissue had undergone myxomatous change.

OSTEOID SARCOMA; GIANT CELL SARCOMA

A variety of descriptive names have been coined for the tumor now to be discussed. It is one rich in polymorphous cellular elements, the most characteristic of which is a large giant cell having as many as twenty-five to sixty nuclei. These cells have been likened by some writers to those of the epulis tumor; by others, to osteoclasts. By the French they have been called *myéloples* and by the early English writers "myeloid cells." In addition to cells, these tumors may have a dense fibrous stroma and, in the most typical cases, osteoid tissue containing cells resembling osteoblasts. Decision as to cases belonging in this group proved difficult because many appearing for other reasons to do so lacked descriptions of osteoid tissue. This of course may have been due to the fact that such tissue was absent. However, a recent experience of one of us (A. R.) demonstrated that osteoid can be easily overlooked, for in a case being studied it was not found until many sections from diverse parts of the tumor had been prepared. This led us to the belief that absence of a description of osteoid was not sufficient grounds for excluding a tumor from membership in this group, and our table is compiled accordingly. Hartmann and his co-workers apparently had the same thought, for, despite the fact that 1 of their patients had osteoid and 2 did not, they nevertheless considered the cases of all 3 as identical. Thus grouped, there were 25 cases, 10 with osteoid tissue. In the remainder it was either absent or, if present, unobserved or not described.

The age distribution of the patients can be gathered from table 6. Of interest is the fact that in many instances the tumor had been present for many years (thirty in 1 instance). In general tumors of long standing grew slowly, either progressively or periodically. Some grew rapidly in the latter part of their course, while others, especially those recently described, grew rapidly from the time they were first noticed. The principal symptom was a sense of mass. Several tumors became adherent to the skin and ulcerated. In a few instances the growth softened and fluctuated. It was not unusual for the skin overlying the tumor to become violaceous and for the veins to become prominent. The modes of treatment varied from simple excision

to radical surgical procedures. None seemed to affect the ultimate course, for in cases in which data were available they showed the outcome to be invariably fatal. Recurrence occurred within five months and death within twelve to fourteen months or earlier.

Grossly the tumors were characteristically circumscribed and in some cases encapsulated. Cysts filled with disintegrated hemorrhagic material were observed in many cases. The preserved solid portions were usually gray, reddish gray and soft. Their size varied from that of a small walnut to as large as 30 by 28 by 18 cm., and they weighed up to 4,500 Gm.

The histologic features have already been mentioned.

In cases of neglected tumor the growth infiltrated the thoracic cage. In cases in which treatment was given the tumors frequently recurred in the scar. The lungs were the usual site of metastasis. In 1 case metastases were found in the heart.²⁰ In cases in which it was possible to study the metastases and recurrences, the tumor reproduced the parent growth grossly and microscopically. The same cystic changes were seen. Also present were the characteristic giant cells and spindle cells, and, finally, even osteoid was reproduced.

MIXED TUMOR

Mixed tumor has been infrequently reported. The majority of the reports appearing in the literature have been contributed by French investigators, and it was they who gave them the name of *tumeurs mixtes*. The tumors may involve either breast, are circumscribed and freely movable and have attained sizes up to that of a fist. Only one²¹ seems to have grown rapidly from the time it was discovered and to have recurred after removal. The chief characteristic of the tumor is the presence of cysts lined with stratified squamous epithelium. Some cysts contained keratin. In 1 case hair follicles were present.²² In another there was, in addition, tissue resembling giant cell sarcoma.²¹ Two contained cartilage²³ and 1 osteoid tissue.^{23b} One tumor appeared to be fibroadenoma^{23b} in which epidermoid cysts were also observed.

20. Stillings, H.: *Deutsche Ztschr. f. Chir.* 15:247, 1881.

21. Nadal, P.: *Bull. et mém. Soc. anat. de Paris* 85:616, 1910.

22. Gioia, T., and Bianchi, A.: *Semana méd.* 2:1193, 1930.

23. (a) D'Allaines, F., and Hiely, J.: *Ann. d'anat. path.* 5:361, 1928. (b) Dubouché, H.: *Montpellier, J., and Laffargue, P.: Algerie méd.* 30:570, 1934.

TERATOMA AND CHONDROLIPOMA

Two tumors of particularly rare occurrence are teratoma and chondrolipoma, only 1 of each being reported: In 1923 McIver²⁴ described in a 60 year old woman a tumor, which in three months grew from the size of a walnut to that of an orange. After removal it proved to be spheroidal, and in it was an alveolar process with teeth. On microscopic examination, osteoid, cartilage and connective tissue were also found. In 1906 Sick²⁵ noted in a 72 year old woman a mass composed of cartilage and fat which he

tumor was the size of a goose egg, circumscribed and composed of fibrous tissue, fusiform cells and cartilage. His description of the carcinomatous elements was not clear. Von Hacker,²⁶ who conducted the pathologic study of Lange's tumor, concluded that the specimen was a mixed tumor containing cartilage and bone which doubtless originated in a cystadenoma of the breast and parts of which later changed to carcinoma. Gross described a circumscribed tumor composed of bone in which elements of carcinoma were present. He felt that the primary growth

TABLE 7.—Mixed Tumor

Author	Year of Publication	Age of Patient	Tumor First Discovered	Symptoms	Treatment	Follow-Up
Lecène; Bull. et mém. Soc. anat. de Paris 70: 698, 1904	1904	54	2 mo.	Mass	Mastectomy; axilla cleared	None
Nadal; Bull. et mém. Soc. anat. de Paris 85: 616, 1910	1910	44	2 mo.	Mass	Mastectomy	Recurrence in 7 mo
D'Allaines (case 1) and Hiely (case 2): Ann. d'anat. path. 5: 361, 1925	1925	19	1 yr.	Mass	Excision	None
Gioia and Bianchi: Semana méd. 2: 1193, 1930	1930	45 (man)	No history	None
Dubouché and others: Algérie méd. 30: 570, 1934	1934	19	Many months	Mass	Excision	None

TABLE 8.—Ossifying-Chondrifying and Giant Cell Tumor Associated with Carcinoma

Author	Year	Age	Onset	Symptoms	Treatment	Enchondroma and carcinoma	Follow Up
Wagner: Arch. d. Helik. 2: 275, 1861	1861	53	2 yr.	Mass	Excision	Enchondroma and carcinoma	Well at 4 mo
Lange: M. Rec. 20: 161, 1881.....	1881	51	20 yr.	Mass	Mastectomy; axilla cleared	Osteochondroma and carcinoma	None
Lucas: Am.-J. M. Sc. 94: 494, 1887....	1887	74	6 mo.	Mass	Mastectomy	Osteoma and carcinoma	None
Coen: Boll. d. sc. med. di Bologna 2: 302, 1891	1891	51	9 yr.	Mass	Excision	Osteochondroma and carcinoma	None
Takano: Arch. f. klin. Chir. 103: 155, 1913-1914	1914	49	3 mo.	Mass	Radical	Carcinoma; chondrosarcoma	None
Kreibitz: Virchows Arch. f. path. Anat. 256: 42, 1925	1925	50	Several months	Mass	Mastectomy	Osteosarcoma and carcinoma	None
Biehl: Beitr. z. Klin. Chir. 140: 39, 1929	1927	55	8 mo.	Mass	Radical	Osteoid sarcoma and carcinoma	None
Budd and Breslin: Am. J. Cancer 31: 207, 1937	1937	59	29 yr.	Mass	Excised	Carcino-osteogenic sarcoma	4 yr post operation, well; type of carcinoma not stated
Tudhope: J. Path. & Bact. 48: 492, 1939	1939	63	3 yr.	Mass; pain	Radical	Osteoid chondrosarcoma and carcinoma	None

diagnosed as chondrolipoma. Grossly the tumor was found to be encapsulated and to resemble a fibroadenoma.

OSSIFYING-CHONDRIFYING AND GIANT CELL TUMOR ASSOCIATED WITH CARCINOMA

The cases in this group, like those in the others, represent a rare form of neoplasm. Wagner entitled his report, "A Case of Enchondroma and Carcinoma of the Breast." The

had originally been a fibroadenoma. The tumor in Coen's case was largely bone, with some cartilage and epithelial elements—the latter giving it a resemblance to alveolar carcinoma. Takano described a tumor composed of two elements, carcinoma and sarcoma. Also present were foci of cartilage. The lymph nodes in his case contained adenocarcinoma. Kreibitz summarized his case thus: "For the most part the tumor is osteosarcoma in which there are present fibroma, cavernoma, and two foci of carcinoma." From Biehl's report we gather

24. McIver, M. A.: Ann. Surg. 77:354, 1923.

25. Sick, C.: Jahrb. d. Hamb. Staatskrankenanst. (1906) 11:17, 1907.

26. von Hacker, V. R.: Arch. f. Klin. Chir. 27: 11, 1882.

"The tumor contained numerous giant cells, polymorphous elements, cartilage, osteoid and carcinoma." Budd and Breslin reported on a tumor part of which was osteogenic sarcoma and part carcinoma. In places these elements were intimately intermixed. Typical epulis-like cells were present.

CARCINOSARCOMA

It is our intention, not to review the literature on carcinosarcoma, but only to note that in some of the reports it is stated that the sarcomatous portion of the growth contained epulis-like cells in large numbers as well as spindle and polymorphous cells, so that there was a strong resemblance to osteoid giant cell tumor. In this group fall the cases of Billroth,²⁷ Fox,²⁸ Helwig,²⁹ Schlagenhauser³⁰ and possibly that of Wilensky.³¹

COMMENT

A group of cases of osteogenic and chondrogenic tumors arising in the breast have been studied. As can be seen from the relatively few reports which have appeared in the literature since 1700, their occurrence in human beings has been uncommon. In contrast, such tumors were found more frequently in breasts of lower mammalia (dogs, goats, cows). In 1860 Virchow³² stated that chondroma was unusually frequent in dogs. In 1910 Glendining³³ likewise reported fibrochondroma, ossifying chondroma and chondrifying fibrosarcoma in dogs. More recently Allen^{17c} corroborated Virchow and Glendining, reviewed the literature, and added 4 more cases of canine tumor and 1 of a similar tumor occurring in a human female.

When individual cases of chondroma, osteogenic sarcoma, giant cell tumor and the others are compared one with the other, no interrelationship may be seen. However, when all the cases are studied and viewed as a whole, basic similarities become apparent. Then such differences as do exist appear to be due to varying

degree of development of the different tumor elements or to the fact that some one element has developed either not at all or so slightly as to escape notice. This is well illustrated by a study of individual reports. Thus Guérin presented his case as an instance of typical osteoid sarcoma, which in truth it appears to be, except that a small amount of cartilage was present. The growth observed by Morton was described by him as composed of cartilage and a moderate number of spindle cells and large, multinucleated giant cells. Only after a committee restudied his case was osteoid tissue noted. In Raso's patient the primary tumor contained cartilage. In the metastasis there was, in addition, cartilage undergoing ossification. Thus a tumor which at first seems to belong in a certain category is later grouped in another because of added observations. Certain threads of similarity relate these seemingly different tumors to each other. In almost all, for instance, the same cellular components are found—spindle, polymorphous and large multinuclear giant cells. Furthermore, in many cases the parent tumor appears to have been a fibroadenoma. So, to us at least, it seemed that a particular tumor could properly be classified as belonging to several groups. For this reason it is our opinion that, however a given case may be classified, it is sound judgment to regard all these cases as related.

References to the fact that portions of tumors presented the picture of fibroadenoma were found in the earliest writings. Later observers swelled the literature with new cases. The following is a tabulation of the types of tumor with the number of cases of each type in which fibroadenoma was detected:

Types	Number of Cases
Chondroma	1
Osteochondroma	1
Osteochondrosarcoma	2
Chondrosarcoma	1
Mixed tumor	3
Giant cell tumor.....	10

Some of the fibroadenomas were intracanalicular and others pericanalicular. In his case 3, Stilling noted a small circumscribed fibroadenoma adjacent to the giant cell tumor. From this he postulated that the former probably arose in a fibroadenoma. In the breast described by Desmarest and his associates, five circumscribed masses were found, four fibroadenoma and the fifth a giant cell tumor. In case 3 of Hartmann and associates a giant cell tumor appeared eight years after a fibroadenoma was removed from the breast. Review of the slides from the first

27. Billroth, T., and Luecke, A.: *Handbuch der Frauenkrankheiten*, Stuttgart, F. Enke, 1886, vol. 3, p. 58.

28. Fox, S. L.: *Ann. Surg.* 100:401, 1934.

29. Helwig, F. C.: *Carcinoma of Breast Combined with Giant Cell Sarcoma*, *Arch. Path.* 4:162 (Aug.) 1927.

30. Schlagenhauser: *Zentralbl. f. allg. Path. u. path. Anal.* 17:385, 1906.

31. Wilensky, A. O.: *Proc. New York Path. Soc.* 19:113, 1919.

32. Virchow, R.: *Die krankhaften Geschwülste*, Berlin, A. Hirschwald, 1863, vol. 1, p. 134.

33. Glendining, B.: *Arch. Middlesex Hosp.* 19:198, 1910.

growth revealed, after careful study, the presence of large multinucleated giant cells. In Pillier's case two tumors were present. One was a fibroadenoma and the other a giant cell tumor. The presence of these fibroadenomas led many authors to conclude that in their case at least the parent growth was the fibroadenoma and that from its tissues cartilage, osteoid, bone and carcinoma had developed.

Following this train of thought, one begins to wonder whether, in those instances in which tumors were observed for long periods, fibroadenoma did not precede the stage of mixed tumor. The mere fact that fibroadenoma was not described does not mean that it was absent in these cases. This was impressed on us by a case which we studied in which intracanalicular fibroadenoma was demonstrated only after the entire tumor was subjected to sectioning.

A word should be said on the life cycle of these tumors as a group. In most cases they were present many years, growing slowly and progressively. Others remained stationary for long periods, after which they proceeded to grow again at a rapid rate. Though most of the tumors remained circumscribed, freely movable and nonadherent, a few eventually ulcerated through the skin and fungated outward. When neglected, they infiltrated through the chest wall into the thoracic cage. No matter what form of surgical treatment was employed—excision, mastectomy or radical—in many cases metastasis followed. Degenerative phenomena in the tumor were not uncommon, these consisting of cystic change, calcification, myxomatous degeneration and necrosis.

Since follow-up studies were lacking in many instances, the complete number with recurrence, metastasis and fatal outcome cannot be given. Of the total group of enchondromas there were data concerning recurrence in 1 case only. This occurred six months after operation. The recurrence reproduced cartilage, as had the parent tumor. Of the chondrosarcomas five recurred in six to nine months, and all the patients were dead in ten to twenty-four months after surgical treatment. Two recurrences were studied histologically and were found to be similar to the parent growth. Both also showed distant metastases to lung, skin and gluteal muscles. There were no data on the osteochondromas. Osteochondrosarcoma proved to be extremely malignant, 6 patients having recurrences in six to ten months and 5 dying one year after first observation. The recurrent and metastatic tumor reproduced bone and cartilage in addition to the pleomorphic cellular elements present in the

parent tumor. Of the growths labeled "mixed tumor" one recurred in seven months. Two of the patients with osteosarcoma died of their tumors one and two years respectively after operation. The giant cell tumors proved to be particularly vicious; fourteen recurred in a few months and caused death in seventeen months. In Stilling's case which came to autopsy there was disclosed a metastasis to the heart. This was a typical giant cell tumor with osteoid tissue. In the case of Moure and De Jong metastasis was demonstrated in the lung. In many of the remaining cases there also appeared to be pulmonary metastases, but, unfortunately, there were no autopsies to prove it. In the case of Jessup, lymph nodes were involved by tumor. The only other type with metastasis to lymph nodes was that associated with carcinoma.

There is considerable discussion in the literature regarding the histogenesis of these tumors. Very early some authors discussed the possible presence in a dormant state of skeletal tissue extruded from rib or clavicle and considered whether such inclusions might at a later date serve as the seed for tumor. This hypothesis has not progressed beyond the phase of theoretic possibility.

Another group has advanced for consideration the possibility of a teratomatous origin. Again, proof of this has not been forthcoming. In all the literature reviewed we could find only 1 example of teratoma of the breast.

The most widely supported view is that ascribing to the tumors a metaplastic origin. It has been demonstrated with reasonable conclusiveness that osteoid and bone may arise in hyalinized collagenous elements.³⁴ The demonstration of chondroid anlage is less clear. In his study on canine tumor, Allen has offered proof of its origin in adult epithelium as well as in mesenchymal cells.

There are differences of opinion as to the nature of the cellular elements of these tumors. Most investigators have taken it for granted that the spindle and polymorphous cells are true sarcoma cells; others are convinced that the giant cells are osteoclasts and that the polyhedral cells within and about the bone are osteoblasts. After study of the material from the cases of Jessup and of Budd and Breslin,³⁵ Ewing³⁶ expressed his view that the cellular components were car-

³⁴ Binkley, J. S., and Stewart, F. W.: Morphogenesis of Extraskelatal Osteogenic Sarcoma and Pseudo-Osteosarcoma, *Arch. Path.* 29:42 (Jan.) 1940.

³⁵ Budd, I. W., and Breslin, F. J.: *Am. J. Cancer* 31:207, 1937.

³⁶ Personal correspondence with Budd and Breslin.³⁵

cinoma. At a later date Stewart, restudying slides from the case of Budd and Breslin, came to the same conclusion. Mallory and Masson,³⁶ who also studied material from this case, felt that the tumor was sarcoma. One fact brought to the foreground by our review which may lend support to their belief is the total absence of metastasis to lymph nodes, that in Jessup's case being the sole exception.

CONCLUSION

Tumors characterized by bone formation, cartilage, fibrous tissue and pleomorphic cells—

thus strongly simulating osteogenic and chondrogenic tumors—occur in the breast.

These tumors are essentially malignant.

Long-standing fibroadenoma is in many cases the parent growth from which they arise.

The osteoid and bone elements probably arise by metaplasia from hyalinized collagen. The mode of origin of cartilage is less clear.

The nature of the cellular component has evoked divergent opinions, some authors saying that it is carcinomatous and others that it is sarcomatous.

METABOLIC ALTERATIONS FOLLOWING THERMAL BURNS

III. EFFECT OF VARIATIONS IN FOOD INTAKE ON NITROGEN BALANCE OF BURNED PATIENTS

JOHN WINSLOW HIRSHFELD, M.D.; WILLIAM E. ABBOTT, M.D.;
MATTHEW A. PILLING, M.D.; CARL G. HELLER, M.D., Ph.D.*;
FRIEDA MEYER, Ph.D.; HAROLD H. WILLIAMS, Ph.D.;
ALLEN J. RICHARDS, B.S., AND ROBERT OBI, A.B.

DETROIT

In 1926 Davidson¹ demonstrated that severely burned patients excrete abnormally large amounts of nitrogen in the urine, a finding which has been confirmed by other investigators.² Although the existence of this abnormality of protein metabolism in burned patients has been well established, its mechanism is not understood. nor is there much information regarding the means of preventing or compensating for this destruction of body protein. The present study was undertaken to obtain more information about the change in protein metabolism in burned patients. It was planned to correlate the nitrogen balance of patients on various diets with the urinary excretion of 17-keto steroids, cortin-like substances, gonadotropins and estrogens. The purpose of this paper is to present studies on the nitrogen balance of 23 patients; the data on the endocrine changes in these patients will be presented elsewhere.

* Present address: Department of Internal Medicine, University of Oregon Medical School.

From the Departments of Surgery and Internal Medicine, Wayne University College of Medicine, and the Divisions of Surgery and Internal Medicine, City of Detroit Receiving Hospital (Dr. Hirshfeld, Dr. Abbott, Dr. Pilling, Dr. Heller and Dr. Meyer), and the Research Laboratory, the Children's Fund of Michigan (Dr. Williams, Mr. Richards and Mr. Obi).

This work was carried out in part under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and Wayne University. It was also supported in part by grants from the Theodore A. McGraw Fund and from Frederick Stearns & Company, Detroit.

1. Davidson, E. C.: Sodium Chloride Metabolism in Cutaneous Burns and Its Possible Significance for a Rational Therapy, *Arch. Surg.* 13:262-277 (Aug.) 1926.

2. (a) Lucido, J.: Metabolic and Blood Chemical Changes in a Severe Burn: A Case Report, *Ann. Surg.* 111:640-644, 1940. (b) Taylor, F. H. L.; Levenson, S. M.; Davidson, C. S.; Adams, M. A., and MacDonald, H.: Abnormal Nitrogen Metabolism in Burns, *Science* 97:423, 1943. (c) Taylor, F. H. L.; Levenson, S. M.; Davidson, C. S., and Browder, N. C.: Problems of Protein Nutrition in Burned Patients, *Ann. Surg.* 118:215-224, 1943.

MATERIALS AND METHODS

A ward of four beds with an adjoining workroom was established, and the patients were under the care of nurses trained in the methods of collection. Although in general the periods of metabolic study were five days, in a few instances shorter or longer periods were employed for some special reason. Metabolic studies were usually instituted within a few hours of the injury, but since some of the patients were intoxicated and uncooperative on admission to the hospital, it was occasionally necessary to postpone the first metabolic period. The first few patients were given a diet considered adequate for the maintenance of weight and nitrogen equilibrium during minimal activity. The diet was planned so that approximately 20 per cent of the calories was derived from protein, 20 per cent from fat and 60 per cent from carbohydrate. Subsequent patients received a diet of the same composition but in larger amounts. The amount of food consumed was determined by weighing the uneaten portion. A duplicate of the diet actually eaten by the patient was weighed and saved for nitrogen analysis. Liquid food was measured in graduated cylinders, and aliquots were removed for analysis.

The diet was planned to give the patients an equal quantity of nitrogen each day. Inasmuch as ordinary food varies considerably in nitrogen content, a synthetic diet of uniform composition was given by tube whenever possible. Generally administration of the diet started during the acute phase of the burn, when it is difficult to persuade patients to eat, and was continued as long as the tube was tolerated. The synthetic diet was composed of Nutramigen,³ Amigen,² Dextri-Maltose³ and vitamins,⁴ in varying proportions. With subsequent patients a diet of egg-nog and orange juice was employed instead of the synthetic diet.

The synthetic and egg-nog diets were supplemented with ascorbic acid, 200 mg.; nicotinic acid, 40 mg.; thiamine hydrochloride, 4.5 mg.; riboflavin, 2 mg., and percomorph liver oil, 5 drops. The diet of conventional food was supplemented with ascorbic acid, 100 mg.; thiamine hydrochloride, 4.5 mg.; riboflavin, 6 mg.;

3. Supplied by Mead Johnson and Company, through the courtesy of Dr. Warren M. Cox Jr., and Mr. R. J. McElroy. "Nutramigen is a food composed of Dextri-Maltose (maltose and dextrins), Amigen, olive oil arrowroot starch, calcium gluconate, brewers' yeast powder and minerals. Amigen is a dried enzymic digest of purified casein and pork pancreas containing amino acids and polypeptides." (Mead Johnson and Company).

4. Supplied by Merck & Co., Inc. through the courtesy of Dr. D. F. Robertson, and by Mead Johnson and Company, through the courtesy of Dr. Warren M. Cox Jr. and Mr. R. J. McElroy.

nicotinic acid, 30 mg., and 4 drops of blended oil containing vitamins A and D, with a potency of 4,250 U.S.P. units of vitamin A and 425 U.S.P. units of vitamin D per gram. One patient (D. H.) received 400 mg. of ascorbic acid, 10 mg. of thiamine hydrochloride, 10 mg. of riboflavin, 60 mg. of nicotinic acid, 100 mg. of pyridoxine, 100 mg. of calcium pantothenate and 8 drops of percomorph liver oil for the first ten days, and 100 mg. of ascorbic acid, 2 mg. of thiamine hydrochloride, 3 mg. of riboflavin, 20 mg. of nicotinic acid, 25 mg. of pyridoxine, 25 mg. of calcium pantothenate, and 3 drops of percomorph liver oil for the remainder of her stay in the hospital.

All nitrogen-containing material given intravenously, such as plasma, whole blood and casein hydrolysate,⁵ was measured, and an aliquot was saved for nitrogen analysis. The figures for the oral and the parenteral intake of nitrogen therefore represent values obtained by actual analysis of the food and of parenteral fluids. The caloric intake was calculated from standard food tables.

The patients voided or were catheterized at the beginning of the first metabolic period and at the end of each subsequent period. Retention catheters were employed for the patients with burns of the perineum and for those who were too ill to cooperate in securing all samples of urine. The urine voided during each twenty-four hours was pooled in a large bottle and stored in the ice box. At the end of each twenty-four hours the volume was measured and an aliquot removed for chemical analysis. The aliquots were stored in the ice box under toluene, and, except when daily determinations were made, the aliquots for five days were pooled. The remainder of the urine was saved for hormone assays.

The exudate from the burned area was collected and analyzed according to a method previously described.⁶ Dressings were applied at the beginning of each metabolic period and with a few exceptions were changed at the conclusion of the period. It was not feasible to collect the exudate from every patient. Carmine was employed to mark the feces, which were pooled for each period and analyzed for nitrogen. If the patient vomited, the vomitus was collected and the nitrogen content determined. The methods of preparation and analysis of the metabolic specimens have been previously described in detail.⁷

Lack of knowledge regarding the utilization of nitrogen administered in the form of transfusions of blood or plasma⁸ makes it difficult to know how it should be considered in estimating the nitrogen balance. For this reason, in determining the balance, nitrogen given intravenously as blood or plasma was arbitrarily omitted. However, the amount of nitrogen derived from this source is presented in column 10 of the table.

RESULTS

Only rarely do burned patients have a desire for more than minimum quantities of food. Our patients were able to consume a diet slightly above

their basal caloric requirement, but frequently when larger quantities of food were given, nausea, vomiting, diarrhea and mental confusion resulted. These symptoms were usually encountered in the first week. They occurred regardless of the type of food but were most pronounced in patients receiving the synthetic diet by tube. Whether the symptoms were produced by excessive amounts of amino acids, calories or water is not known. Sometimes these patients vomited enough to lower materially their caloric and nitrogen intake (G. R., section C of table), a circumstance that necessitated revision of their diet. For these reasons the protein, carbohydrate and caloric intake of the patients, especially those who had forced feeding, was not as constant as desired.

Of the patients whose burns exceeded 30 per cent of their body surface, only 2 (C. W. and M. Mc.) lived ten days or longer. One patient (F. H.) with 64 per cent of her body burned, lived for seven and one-half days. The other patients (D. B. and E. B.) with 30 per cent or more of the body surface burned did not survive long enough to permit any conclusions to be drawn from a study of their nitrogen balance.

All the patients excreted abnormally large quantities of nitrogen in the urine. The results of the urinary nitrogen partition will be reported in a subsequent publication. They are not in agreement, however, with the results of Taylor and associates,^{2b} who found in some of their patients "large increases in the residual nitrogen of the urine, both in the absolute amount and in the percentage of the total nitrogen excreted."

Except for a few patients who received abnormally large quantities of protein and carbohydrate, all the patients were in negative nitrogen balance. The negative balance was usually most pronounced during the first ten days and gradually decreased thereafter (table). The patients who were in pronounced negative nitrogen balance lost weight, and some became visibly emaciated. As one would expect, the nitrogen deficit did not reflect the changes in weight. For example, R. Mc. lost approximately 19.4 Kg. in eighteen days, while the nitrogen lost, which did not include that lost from the wound, was only 194.5 Gm., or, in terms of muscle,⁹ about 6 Kg.

It does not appear that there is a direct correlation between the extent or depth of the burn and the loss of nitrogen in the urine. This lack of correlation was probably due to many variables such as the type of bacteria that infects the burned area, the state of the patient's nutrition before the burn, the degree of muscular develop-

9. Muscle is assumed to be 20 per cent protein, and the factor for converting nitrogen to protein is 6.25.

5. Supplied by Frederick Stearns & Company, Detroit.
6. Hirschfeld, J. W.; Williams, H. H.; Abbott, W. E.; Heller, C. G., and Pilling, M. A.: Significance of the Nitrogen Loss in the Exudate from Surface Burns, *Surgery* 15:766-773, 1944.

7. Macy, I. G.: Nutrition and Chemical Growth in Childhood, Springfield, Ill., Charles C Thomas, Publisher, 1942, vol. 1.

8. Elman, R.: Maintenance of Nitrogen Balance by the Intravenous Administration of Plasma Proteins and Protein Hydrolysates, *Physiol. Rev.* 24:372-389, 1944.

Patient; Sex; Age	Per Cent of Body Burned		Location	Days After Burn	Weight In Kg.	Average Tempera- ture per Period, F.	Estimated Basal Caloric Require- ment *	Caloric Intake per Day †	Calories per Kg. per Day ‡	Nitrogen Intake, Gm. per Day	
	Total	Degree								Oral	Parentera
A											
J. C. M 46 yr.	9	5	Hands and forearms	1-5 6-10 11-15 16-20 21-24	99.2 98.4 98.4 98.4 98.4	2,205 F 2,274 F 2,078 F 1,788 F 1,788 F	9.9 11.8 11.5 10.8 10.9
B. P. M 40 yr.	10	4	Face, neck, arms and back	2-6 7-11 12-15 16-20 45.5	100.8 100.5 99.0 98.9	1,267.2	1,755 F 1,755 F 1,854 F 1,855 F	26.6	9.1 9.6 9.2 9.6	2.4 (plasma)
R. H. M 16 yr.	10	6	Hands and forearms	(admission 62.4) 1-5 6-10	56.8 53.4	99.6 98.9	1,626.6	1,704 S 1,704 S	27.3	9.8 9.4
R. Mc. M 47 yr.	22	22	Legs, thighs, buttocks, genitalia and perineum	(admission 73.2) 5-9 10-12 14-18 19-22 53.8	100.4 99.1 100.9 100.6	1,514.4	2,180 F 2,628 F 2,028 F 2,724 F	29.8 37.3	5.8 11.0 11.3 14.1 5.3 (amino acids)
H. S. M 47 yr.	21	6	Face, neck, arms and hands	1-5 9-15 14-18 19-23 24-27 28-32 33-37	80 63.5	100.2 100.4 100.6 99.7 98.2 98.2 98.3	1,612.8	2,144 S 2,505 S & F 2,528 F 2,528 F 2,559 F 2,617 F 2,569 F	26.8 31.2	14.9 14.8 13.9 13.5 16.4 15.8 17.2	1.6 (plasma)
C. W. M 42 yr.	23	25	Face, neck, arms, shoulders and back	1-5 6-10	101.4 102.3	1,675 F 1,892 F	8.4 10.8	6.8 (plasma)
E. L. F 35 yr.	8	8	Breast, arm and shoulder	32-36 37-41 42-47	98.8 98.7 99.9	1,204 F 1,497 F 1,255 F	7.4 8.8 5.7	20.0 (blood)
I. V. F 22 yr.	16	1	Arms, forearms, scalp and neck	1-5 6-10 11-15	77.5 78.8	99.3 98.9 98.9	1,560.0	2,092 S 2,550 F 2,550 F	26.2 32.9	12.5 20.5 21.6
M. Mc. F 40 yr.	32	2	Abdomen, chest, back, buttocks, thighs and external genitalia	1-5 6-10 11-15 16-20 21-25 26-30	100.9 101.6 101.2 101.1 99.8 99.4	1,338 F 1,312 F 1,278 F 1,348 F 1,344 F 1,276 F	7.8 8.0 7.9 7.8 8.0 7.2	4.1 (plasma)
E. B. F 41 yr.	84	Most of body	1	59.1	100.4	1,255.2	2,134 S	36.1	17.7 49.1	(plasma)
B											
A. M. M 51 yr.	6.5	0	Hands and forearms	1-5 6-10 11-15 16-20 21-25 26-30 32-38	60.0 63.4 62.5 62.5 63.9 63.0	99.4 98.5 97.7 97.9 97.5 97.5 97.9	1,360.8	4,889 S 4,828 S 2,823 F 2,823 F 2,823 F 2,874 F 2,860 F	73.2 75.5 49.9	25.4 26.3 20.3 20.5 19.5 23.4 21.0	1.4 (plasma)
I. G. M 25 yr.	12	2	Hands, face, neck, legs, thighs and shoulders	1-2 6-10 14-16 21-25	85.4	101.0 99.5 98.8 98.0	1,764.0	6,737 S 4,671 F 4,819 F 2,339 F	78.8 54.7 27.4	47.7 41.7 29.5 21.7	4.6 (amino acids) 5.6 (plasma)
B. W. F 58 yr.	9	4	Hand, forearm, shoulder and chest	3-7 10-11	63.6	100.2 101.1	1,257.6	4,268 S 4,268 S	67.1	26.0 22.5
C. L. F 32 yr.	10	1	Face, forearms, shoulders and hands	1-5 6-10 11-15 16-20 26-30	77.7 77.2 77.9 77.0	101.6 100.7 99.1 99.0 98.6	1,455.6	4,556 S 3,000 S 3,000 S 3,353 S & F 2,576 F	58.6 38.6	26.7 29.8 29.8 20.7 23.0	4.6 (plasma)
P. R. F 32 yr.	18	0	Face, thighs, hands and arms	3-7 8-13 14-17	82.9	100.9 99.4 98.8	1,533.6	6,250 S 3,445 S 3,563 F	76.6 41.6	22.7 23.7 22.5
D. B. F 16 yr.	63	At least half of body	Back, legs, arms, face and chest	1-4	101.2	4,212 S	27.6	12.2 (plasma plus whole blood)
F. H. F 17 yr.	64	At least half of body	Arms, legs, back, thorax, face, neck, buttocks and abdomen	1-5 6-7	53.2	102.1 103.3	1,234.4	3,951 S 3,973 S	74.3	24.6 23.5	9.4 (plasma)
106											

Three Patients with Thermal Burns

Average Daily Volume of Urine, Cc.	Nitrogen Output, Gm. per Day				Total	Nitrogen Balance (Excluding Nitrogen Administered as Blood or Plasma)	Comments
	Urine	Feces	Wound	Emesis			
A							
1,235	20.9	1.2	2.7		24.8	-14.9	Gasoline fire burns; left hand healed in 15 days; grafts on right hand and forearm on 25th day, with 100% take
1,210	15.9	0.5	1.3		20.7	- 8.9	
1,000	14.7	2.4	1.4		18.5	- 7.0	
1,070	11.4	2.7	1.4		15.5	- 4.7	
1,350	10.7	1.2	0.7		12.6	- 1.7	
1,100	13.0	0.7	2.0		15.7	- 6.6	Chronic alcoholism; fire burn; grafts on third degree areas on 25th day
970	12.5	0.8	2.4		15.7	- 6.1	
840	11.5	0.5			12.0	- 2.1	
1,000	10.5	1.0			11.5	- 1.9	
3,560	18.3	1.5	3.4		23.2	-13.4	Gasoline fire burn; complete healing by 10th day; patient received 95 rat units of antuitrin G $\frac{1}{2}$ on 2d, 3d, 5th, 6th, 7th, 9th and 10th days
2,450	21.1	1.8	0.2		23.1	-13.7	
3,010	20.6	1.5	...	0.7	22.8	-14.0	Chronic alcoholism; fire burn; burns deep; patient died on 62d day
2,688	20.3	1.5		0.9	22.7	-11.7	
2,210	19.6	0.9			20.5	- 9.2	
3,740	22.1	1.3			23.4	- 4.0	
3,160	18.4	3.9			22.3	- 7.4	Fire burn; deep 2d degree burns which healed without grafting in 35 days
3,990	14.9	2.4			17.3	- 2.5	
3,740	16.8	3.8			20.6	- 6.7	
3,650	14.0	Lost		0.3			
1,513	13.4	Lost					
1,500	13.8	Lost					
1,530	12.4	1.5			13.9	+ 3.3	
1,420	22.6	0.4	7.9	...	30.9	-22.5	Fire burns; patient died at end of 10th day
1,610	19.6	0.4	4.6		24.6	-13.8	
1,480	5.9	0.7	1.8	..	8.4	- 1.0	Fire burn; grafts on 37th day, with 50% take
1,480	5.9	1.4	1.6		8.9	- 0.1	
1,200	5.4	1.4	0.6		7.4	- 1.7	
2,020	15.4	2.3	1.2	0.9	19.8	- 7.3	Fire burn; patient 2 months pregnant; wound healed in 15 days except area on forehead, which required grafting
2,030	23.2	0.7	0.2		24.1	- 3.6	
1,970	22.6	1.5			24.1	- 2.5	
4,660	10.7	No feces	10.7	- 2.9	Scalded; burns healed by 20th day, except the areas of third degree burns; grafts on 31st day, with 95% take
3,890	13.6	0.7			14.3	- 6.2	
2,980	14.7	0.7			15.4	- 7.5	
3,040	12.6	1.4			14.0	- 6.2	
3,020	9.8	1.3			11.1	- 3.1	
2,430	9.0	0.5			9.5	- 2.3	
2,500	10.5	2.4	...	0.1	13.0	+ 4.7	
B							
1,210	12.6	6.6	1.8	1.4	22.4	+ 3.0	Burns with hot grease; deep second degree burns, which did not heal until 25th day
1,410	14.3	3.1	1.2	0.3	18.9	+ 7.4	
2,010	15.9	1.8	0.7		18.4	+ 1.9	
1,840	16.5	2.0	0.4		18.9	+ 1.6	
2,100	16.6	2.0			18.6	+ 1.2	
1,600	16.0	2.2		0.1	18.3	+ 5.1	
1,580	15.6	2.3			17.9	+ 3.1	
.....	30.6	4.3	...	6.2	41.1	+ 4.6	Flash burn (illuminating gas)
	27.0				27.0	+14.7	
	26.0				26.0	+13.5	
	23.8				23.8	- 2.1	
1,300	20.8	1.8	...	0.6	23.2	+ 2.8	Fire burn; elderly, mentally confused and incoherent patient, with extremely deep burns; died on 13th day
1,300	18.4	2.4		0.3	21.1	+ 1.4	
2,140	24.8	5.8	...	0.04	30.6	- 6.1	Flash burn (illuminating gas); facial burns healed in 10 days; other areas healed by 20th day except for dorsal aspects of both hands, which were grafted on 23d day, with 100% take
2,750	27.7	1.9		0.1	29.7	- 0.1	
2,480	29.8	2.0			31.3	- 1.5	
2,670	22.8	3.8			26.6	- 4.1	
2,390	17.7	1.7			19.4	+ 3.6	
1,860	21.2	3.7	...	1.9	26.8	+ 2.9	Flash burn (illuminating gas); nearly healed on 17th day
2,200	23.2	3.3		1.0	27.5	- 3.8	
1,725	21.2	3.3			24.5	+ 5.3	
1,932	23.2	2.9	...	0.8	26.4	+ 1.2	Flash burn (illuminating gas); patient died on 5th day
3,190	23.8	1.2	...	0.3	25.0	- 0.4	Fire burn; patient received 96 rat units of antuitrin G $\frac{1}{2}$ daily; died on 7th day
2,475	29.6	1.0		0.3	31.9	- 3.4	

Data on Protein Metabolism in Twenty-

Data on Protein Metabolism in Twenty

Patient; Sex; Age	Per Cent of Body Burned		Location	Days After Burn	Weight in Kg.	Average Tempera- ture per Period, F.	Estimated Basal Caloric Require- ment*	Caloric Intake per Day †	Calories per Kg. per Day ‡	Nitrogen Intake, Gm. per Day	
	Total	3d Degree								Oral	Parenteral
C											
L. A. M 12 yr.	12	10	Both legs	1-5	40.7	100.5	2,192.6	3,564 S	94.9	25.0
				6-10		100.7		3,684 S		22.5	
				11-15		99.2		3,355 F		17.1	
				16-20		99.2		3,600 F		15.6	
				21-25		99.4		3,654 F		16.0	
				26-29		98.3		1,992 F		15.7	
				(admission 54.1)							
G. R. M 10 yr.	26	22	Both legs and left hand	1-5	33.2	100.4	1,140.0	3,500 S	102.6	19.9	1.6 (plasma)
				6-10	33.4	101.3		3,173 S		16.9	
				11-15	28.6	99.7		3,500 F		19.4	
				16-20		99.0		1,671 F		13.8	
				26-29	30.0	100.6		1,681 F		14.2	
				21-25	30.4	100.9		1,695 F		13.9	
				30-34	28.9	99.2		1,695 F		13.6	
I. S. F 5 yr.	3	5	Back, axilla and right arm	1-5	100.4	601.2	1,031 F	70.7	4.8
				6-10		100.6		1,193 F		4.5	
				11-15		100.3		1,136 F		5.2	
				16-20		99.7		1,108 F		4.9	
				21-25	15.0	98.7		984 F		4.9	
				26-29		98.2		783 F		4.6	
				(admission 17.5)				600 S			
D. H. F 5 yr.	9	4	Right half of back and right hip	1-5	15.2	100.9	745.4	1,132 E	52.6	4.7	1.6 (plasma)
				6-10	18.6	101.8		1,133 E		7.9	
				11-15	17.5	99.9		1,175 E		9.6	
				16-20	17.0	99.8		1,175 E		9.4	
				21-25	16.6	99.3		1,132 E		7.8	
				26-29	17.9						
				(admission 17.5)							
L. W. F 10 yr.	14	10	Right side of trunk	1-5	23.4	101.2	800.4	1,824 S	77.9	10.0	5.0 (plasma)
				6-10	23.4	101.2		1,823 S		11.0	
				11-15		100.5		1,820 S		10.5	
				16-20	21.4	100.9		2,117 S		13.3	
D. R. F 12 yr.	15	Less than 0.5%	Back, arm and buttocks	1-5	40.9	100.3	1,826.4	2,763 F	67.5	16.1	1.5 (plasma)
				6-10		99.8		2,764 S		16.4	
				11-15	42.7	98.5		2,995 S		16.4	

* Estimated basal caloric requirement computed on basis of weight by the formula of Dreyer (The Normal Basal Metabolism in Man, Lancet 2: 239-251, 1920).

† Total calories per day calculated from food tables. F indicates a diet of conventional food; S, a synthetic diet, and E, a diet of egg yolk and orange juice.

‡ Calculated on basis of patient's weight on admission to the hospital.

§ Not a complete collection.

ment, the patient's age and sex, the type of burn and the extent and nature of the shock therapy employed.

The nitrogen lost in the exudate from the burn was measured for 12 patients. The significance of this loss was discussed in detail in a previous communication.⁶ It varied from 7.9 Gm. per day during the first five days in C. W., an adult man whose body surface was 33 per cent burned, to 0.7 Gm. per day for the first five days in I. S., a 5 year old girl whose body surface was 5 per cent burned. In general, the nitrogen content of the exudate from the wound was highest during the first few metabolic periods. It then remained fairly constant unless the burned area decreased in size through spontaneous healing or skin grafting.

The question naturally arose as to whether the nitrogen deficit could be prevented or diminished by feeding diets of high carbohydrate and protein content. In an attempt to answer this question, a number of patients were given a diet containing 54 to 102 calories per kilogram of body weight. The protein content varied from 1.25 to 3.6 Gm. per kilogram.

In contrast to the patients on a diet low in calories and nitrogen, the patients who suc-

ceeded in retaining a high caloric and nitrogen intake maintained, or nearly maintained, their weight, and they lost only small amounts of body protein, as evidenced by a slight nitrogen deficit (sections B and C of table). One patient (A. M.) actually retained nitrogen during the entire period of study, while others were periodically in positive nitrogen balance. The patients with high caloric and nitrogen intakes who were in negative nitrogen balance came into positive balance much sooner than the patients with the lower caloric and nitrogen intakes. Clinically the state of nitrogen balance had no perceptible effect on the rate of wound healing during the time the patients were studied under the experimental regimen.

Although it was possible by means of a high caloric and protein intake to prevent excessive loss of nitrogen and weight, the clinical course of these patients seemed to leave little doubt that forced feeding with the type of diet employed is undesirable, at least during the first ten days after injury.

COMMENT

It has been known for a long time that patients suffering with an acute infectious disease excrete abnormally large amounts of nitro-

Three Patients with Thermal Burns—Continued

Average Daily Volume of Urine, Cc.	Nitrogen Output, Gm. per Day					Nitrogen Balance (Excluding Nitrogen Administered as Blood or Plasma)	Comments
	Urine	Feces	Wound	Emesis	Total		
1,380	19.7	0.6	2.1	2.0	24.4	+ 0.6	Fire burn; grafts on 22d day
1,470	21.7	0.7	1.2	1.5	25.1	— 1.6	
2,169	19.7	1.3	1.8		22.8	— 5.7	
2,520	15.0	1.3	1.8		18.1	— 2.5	
2,340	13.9	2.0			15.9	+ 0.1	
1,820	12.3	2.1			14.4	+ 1.3	
880	15.4	0.6	2.6	4.8	23.4	— 3.5	Fire burn; grafts on 25th day, with perfect take; patient received 96 rat units of antuitrin G [†] on 1st, 2d, 3d, 4th, 5th, 6th, 7th, 8th and 9th days
1,320	17.7	1.4	2.0	6.0	27.1	— 10.2	
1,469	16.4	1.2	2.3	4.1	24.0	— 4.6	
1,690	12.6	1.0		1.3	14.9	— 1.1	
970	9.9	1.6			11.5	+ 2.7	
1,600	7.4	1.2		1.1	9.7	+ 4.2	
1,125	10.1	0.9		1.1	12.1	— 1.5	
710	5.7	1.0	0.7	...	7.4	— 2.6	Fire burn; grafts on 26th day, with complete take
780	5.0	0.4	0.9		6.3	— 1.8	
1,140	4.6	1.1	0.8		6.5	— 1.3	
1,070	4.4	0.7	0.8		5.9	— 1.0	
990	3.5	1.2			4.7	— 0.2	
810	3.4	0.6			4.0	+ 0.6	
1,400	5.1	0.3	1.0	...	6.4	— 1.7	Fire burn; grafts on 27th day, with excellent take
1,300	7.5	0.5	1.1		9.1	— 1.2	
1,460	6.6	0.6	1.2		8.4	+ 1.2	
1,420	7.2	0.3	1.2		8.7	— 0.7	
1,020	4.6	0.4			5.0	— 2.5	
1,620	11.0	0.6	...	1.6	13.2	— 3.2	Fire burn; grafts on 28th day, with 99% take, and on 44th day, with 95% take
1,240	11.5	1.9			13.4	— 2.4	
900	9.4	2.2		0.5	12.1	— 1.3	
590	10.1	1.7		1.7	13.5	— 1.8	
2,240	11.5	2.9	2.5	0.8	17.2	— 1.1	Fire burn; healed in 15 days except for a small area that required grafting, which was done on 16th day
2,250	17.5	1.7	1.4		20.6	— 4.2	
4,130	16.4	1.5	0.6		18.5	— 2.1	

* Does not include nitrogen lost from wound.

† A preparation containing the growth-promoting (somatotrophic) principle derived from the anterior lobe of the pituitary.

‡ Does not include fecal nitrogen.

§ Synthetic diet (no nitrogen was administered orally on first two days).

†† Average 930.

gen in the urine and are in negative nitrogen balance. This has been attributed to the toxic destruction of body protein by bacterial products or to the toxic effect of the breakdown products of injured tissue. Shaffer and Coleman,¹⁰ in 1909, studied this phenomenon in patients with typhoid. They concluded that the loss of nitrogen during the febrile period of this disease could be prevented or compensated for "by the use of diets of high caloric value and especially rich in carbohydrate." Although Shaffer and Coleman apparently were able to decrease the nitrogen loss in patients with typhoid by feeding a diet containing large amounts of carbohydrate, they succeeded in obtaining nitrogen equilibrium in only 1 patient during the early stage of the disease, and then for just a few days. In later studies Coleman and DuBois¹¹ demonstrated that patients with typhoid could not be kept in

nitrogen equilibrium with a caloric intake sufficient to cover their energy requirements. These authors concluded that it was necessary to provide calories 50 to 110 per cent in excess of the energy requirement in order to obtain a positive nitrogen balance. Even with these large caloric intakes it was not possible to reduce the protein metabolism of patients with typhoid to the low level that can be obtained for normal persons¹⁰ on a similar diet. To obtain nitrogen equilibrium it was necessary, in spite of a high caloric intake, to provide 10 to 15 Gm. of nitrogen in the diet. The conclusion seemed inescapable that typhoid increases the rate of protein catabolism.

Cuthbertson¹² observed that similar alterations of protein metabolism occur after fracture and other types of trauma. In a study of the metabolic disturbances following fracture he¹² concluded that it was possible with diets high in carbohy-

10. Shaffer, P. A., and Coleman, W.: Protein Metabolism in Typhoid Fever, *Arch. Int. Med.* 4:538-600 (Dec.) 1909.

11. Coleman, W., and DuBois, E. F.: Calorimetric Observations on the Metabolism of Typhoid Patients With and Without Food, *Arch. Int. Med.* 15:887-938 (May) 1915; The Influence of the High-Calory Diet on the Respiratory Exchanges in Typhoid Fever, *ibid.* 14:168-209 (Aug.) 1914.

12. Cuthbertson, D. P.: Post-Shock Metabolic Response (Arris and Gale Lecture), *Lancet* 1:433-436, 1942.

13. Cuthbertson, D. P.: Further Observations on the Disturbance of Metabolism Caused by Injury, with Particular Reference to the Dietary Requirements of Fracture Cases, *Brit. J. Surg.* 23:505-520, 1936.

drate and protein to decrease the nitrogen loss during the early period after injury but that it was not possible to obtain a positive nitrogen balance. Cope and his co-workers,¹⁴ on the other hand, stated that it was not difficult to obtain a positive nitrogen balance in burned patients of the Coconut Grove disaster when the caloric and nitrogen intake was adequate. A review of their data shows that nitrogen equilibrium was accomplished largely with the use of plasma or blood. It was not accomplished in the early period after injury with food alone. Furthermore, the nitrogen lost in the stools and the exudate was not included by Cope and his co-workers in constructing their tables. One can speculate, therefore, whether most of the patients would not have been in negative nitrogen balance if they had not received large amounts of blood and plasma and if the nitrogen lost from the wounds and in the stools had been considered.

The present data confirm the results of other workers¹⁵ who have found that burned patients excrete large amounts of nitrogen in the urine. The results seem to show also that it is possible to overcome, or at least to diminish, this loss by giving a diet of high carbohydrate and protein content. In practice this is attended with considerable difficulty in the first few weeks after injury because the patients have poor appetites. Whether or not it is desirable or necessary to give normal or slightly increased quantities of food during the acute phase of a burn is not known. There is no doubt, however, that it is necessary at the end of a week or ten days if the patient has an extensive third degree burn. Such a patient faces a prolonged period of illness; and if he is not forced to take food, protein and vitamin deficiencies develop.

More work is required to demonstrate whether this abnormal nitrogen loss in burned patients can be compensated for by the administration of large amounts of protein without the high caloric intake employed. If this is possible, it would be more practical.

The mechanism of the protein loss in these patients has not been definitely established. Albright¹⁶ and Browne¹⁷ expressed the opinion

that it is due to a change in adrenal cortex hormone production and is a pattern of response which the body makes to all types of injury (alarm reaction), as described by Selye.¹⁸

Until the cause of the undesirable effects we observed is determined, it seems wiser not to force food on burned patients during the acute phase but, rather, to provide them only with such food as they desire and can tolerate. Attempts to force large quantities of food at this time apparently result in upsetting the patient. After two or three days have passed, he can be given a moderate diet. If the patient has a severe burn and faces a prolonged convalescence, it is essential to increase the diet as rapidly as can be tolerated, especially in regard to its protein content.

SUMMARY

The nitrogen balance of 23 burned patients was determined by comparing the nitrogen intake with the nitrogen lost in the vomitus, urine, feces and exudate from the wound.

All the patients excreted large amounts of nitrogen in the urine, and, except for a few who received abnormally large quantities of protein and carbohydrate, were in negative nitrogen balance and lost considerable weight.

It was possible to prevent or decrease a negative nitrogen balance and to prevent or diminish loss of weight by feeding diets of high protein and caloric content. However, the diets employed in this study were poorly tolerated during the first few days after injury.

Most burned patients, if allowed to eat only what they desire, will not consume an adequate diet. It is important therefore, after the shock phase of the injury has passed, to insist that they eat sufficient food to maintain proper nutrition.

Dr. Icie G. Macy, director of the Research Laboratory of the Children's Fund of Michigan, and Dr. Arthur H. Smith, professor of Physiological Chemistry, Wayne University College of Medicine, gave advice and counsel during the course of the work.

Louie J. Key, Margaret Lutes, Phoebe Ross, Velva Seigneur and Sarah Thompson gave faithful and careful nursing care, and Gertrude Gall gave dietetic assistance.

Research Laboratory of the Children's Fund of Michigan, Wayne University College of Medicine.

14. Cope, O.; Nathanson, I. T.; Rourke, G. M., and Wilson, H.: Symposium on Management of the Coconut Grove Burns at the Massachusetts General Hospital: Metabolic Observations, *Ann. Surg.* **117**:937-958, 1943.

15. Davidson.¹ Footnote 2.

16. Albright, F.: Cushing's Syndrome. Its Pathological Physiology; Its Relationship to the Adrenogenital Syndrome, and Its Connection with the Problem of the Reaction of the Body to Injurious Agents ("Alarm Reaction" of Selye), in *Harvey Lectures, 1942-1943*, "Alarm Reaction" of Selye), in *Harvey Lectures, 1942-1943*, Lancaster, Pa., Science Press, 1943, vol. 38, pp. 123-186.

17. Browne, J. S. L., in Conference on Bone and Wound Healing, New York, Josiah Macy Jr. Foundation, Dec. 11-12, 1942, p. 55.

18. Selye, H.: The Alarm Reaction, in *Piersol, G. M., Bortz, E. L., and others: Cyclopedia of Medicine, Surgery and Specialties*, Philadelphia, F. A. Davis Company, 1940, vol. 15, pp. 15-38.

INFLUENCE OF ENVIRONMENTAL TEMPERATURE ON SHOCK

H. C. BERGMAN, PH.D., AND MYRON PRINZMETAL, M.D.

LOS ANGELES

A number of experimental observations on the effect of environmental temperature on shock have recently been made.¹ It was observed that extremes of heat and cold have deleterious effects on the survival time of animals in shock.^{1a, b} There have been wide differences of opinion as to the optimal environmental temperatures for shocked persons. Thus, Elman and his co-workers^{1c} recommended a temperature of 75 F., Cleghorn^{1d} 72 F. and Wakim and Gatch^{1e} 85 F. Examination of the data presented by the various authors shows that these variations may be due to study of an insufficient number of temperatures in the region of 65 to 95 F. Likewise, the number of animals employed may not always have been adequate for demonstrating significant responses with small differences in temperature.² It is the purpose of this report to determine in a more complete manner the optimal temperature for decreasing mortality in mice subjected to burn shock and to report observations on the possible mechanism of the effects observed.

Aided by grants from the Blanche May Selden Fund. F. Brice, Mrs. J. Pressman and Mr. and Mrs. Samuel A. Marx.

From the Straus Research Laboratory, Cedars of Lebanon Hospital, and the University of Southern California Medical School, Los Angeles.

1. (a) Blalock, A., and Mason, M. F.: A Comparison of the Effects of Heat and Those of Cold in the Prevention and Treatment of Shock. *Arch. Surg.* 42:1054-1059 (June) 1941. (b) Rosenthal, S. M.: Experimental Chemotherapy of Burns and Shock: I. Methods; II. Effects of Local Therapy on Mortality from Shock, *Pub. Health Rep.* 57:1923-1935, 1942. (c) Elman, R.; Cox, W. M., Jr.; Lischer, C., and Mueller, A. J.: Mortality in Severe Experimental Burns as Affected by Environmental Temperature, *Proc. Soc. Exper. Biol. & Med.* 51:350-351, 1942. (d) Cleghorn, R. A.: The Effect of Different Environmental Temperatures on Survival of Dogs After Severe Bleeding, *Canad. M. A. J.* 49:363-367, 1943. (e) Wakim, K. G., and Gatch, W. D.: The Effect of External Temperature on Shock, *J. A. M. A.* 121:903-907 (March 20) 1943.

2. Prinzmetal, M.; Hechter, O.; Margoles, C., and Feigen, G.: A Principle from Liver Effective Against Shock Due to Burns, *J. Clin. Investigation* 23:795-806, 1944.

3. Prinzmetal, M., and Bergman, H. C.: The Nature of Circulatory Changes in Burn Shock, *Clin. Sc.*, to be published.

The altered hemodynamics in burn shock have recently been studied in this laboratory.³ It has been found that the reduced circulating blood volume in burn shock is due to two separate factors, capillary atony and local fluid loss. By transfusion experiments, it was shown that there is a toxic factor in the blood of burned animals which produces capillary atony. The capillary atony is characterized by an increase in number and diameter of open capillaries. For example, over three times as many open and dilated capillaries were counted in the kidneys of burned rats as in those of nonburned animals. Likewise, there were approximately five times as many open capillaries in the hearts of shocked animals as there were in the hearts of control animals.⁴ This capillary atony, which causes intense congestion of the viscera, is not due to heart failure or to anoxia, since it was shown that capillary congestion begins immediately after severe trauma. Measurement of the hemoglobin retained by the viscera of shocked animals showed an increase in blood content over that of nonburned animals. In these experiments, both control and shocked animals were killed by exsanguination. This was necessary since it was found that if the animals were not exsanguinated, the appearance of the shocked organs was not particularly distinctive. The relative importance of local fluid loss and the toxic factor varied with the character of the burn and the time after trauma. In certain types of burns the factor of local fluid loss was unimportant and the capillary toxic factor accounted for all disturbances. Under other conditions the factor of local fluid loss was operative in the first few hours after trauma but the toxic factor became progressively more significant and later dominated the clinical picture. Likewise, in shock produced by a muscle-crushing injury in dogs,⁵ in which infection is of primary importance, further experi-

4. Prinzmetal, M., and Bergman, H. C.: The Heart in Experimental Shock, *J. Mt. Sinai Hosp.*, to be published.

5. Prinzmetal, M.; Freed, S. C., and Kruger, H. E.: Pathogenesis and Treatment of Shock Resulting from Crushing of Muscle, *War Med.* 5:74-79 (Feb.) 1944.

mentation demonstrates that the same two factors also operate in causing the shock state: the capillary toxic factor, which appears to be most important, and varying degrees of local fluid loss. Preliminary observations made in this laboratory on tourniquet shock indicate that these two factors are also involved in the resulting shock state. The prophylactic effectiveness of liver extract and other compounds has recently been studied in this manner.⁶ The quantitative and qualitative data on the cause of the decreased circulation in shock make possible the application of the same methods to determine reasons for the deleterious influence of certain environmental temperatures on the mortality of burned mice.

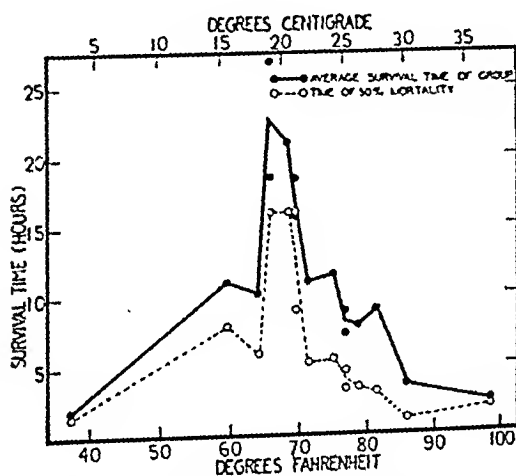


Chart 1.—Effect of environmental temperature on mortality in burn shock. Each point represents 20 to 26 mice, etherized and scalded up to the head at 65 C. for ten seconds, kept in rooms at various constant temperatures. The range of environmental temperatures for optimal survival is 65 to 71 F.

EXPERIMENTAL STUDIES

EXPERIMENT 1.—Effect of environmental temperature on mortality in burn shock.

Groups of 20 to 26 mice, completely anesthetized with ether and burned up to the head in water at 65 C. (149 F.) for ten seconds, were placed in various rooms at different temperatures. This severe burn causes high mortality, with typical clinical and pathologic manifestations of shock.² Each room was maintained at a constant temperature throughout a forty-eight hour period of observation. The mice alive at the

end of this period were arbitrarily assigned a survival time of forty-eight hours. In confirmation of the results of others, it was immediately apparent that extremes of heat (98 F.) and of cold (37 F.) were associated with a great increase in mortality. We therefore performed most of our experiments at temperatures between 60 and 85 F. A total of 399 mice were used to obtain the data represented in chart 1. It can be seen that the optimal temperature range for survival is between 65 and 71 F. At 75 F. the mortality is definitely higher than at 71 F. At 85 F. most of the animals died rapidly.

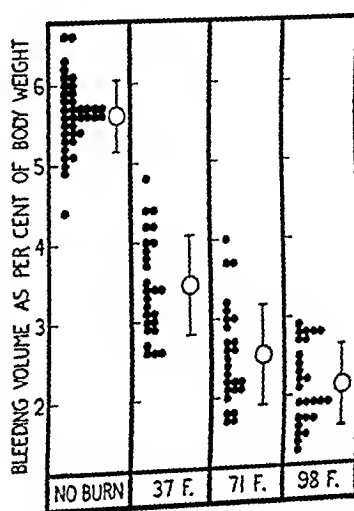


Chart 2.—Effect of environmental temperature on bleeding volume. Mice anesthetized and burned up to the head at 61 C. for ten seconds were divided into three groups and placed in rooms at 37, 71 and 98 F. respectively. Bleeding volumes were taken from one-half hour to two hours after trauma. Each dot represents the bleeding volume of 1 mouse. The large circles represent the mean response; the total length of the vertical lines equals two times the standard deviation of a single observation; the small horizontal lines at the ends of the vertical lines have a length equal to the standard error of the mean. It can be seen that the bleeding volume of shocked animals kept at ordinary room temperature (71 F.) is reduced as compared with that of nonshocked animals. There is a further reduction of the bleeding volume of burned animals kept at 98 F. The reduction of the bleeding volume at 37 F. is significantly less than at 71 F.

EXPERIMENT 2.—Effect of environmental temperature on bleeding volume.

Determinations of bleeding volumes were made on burned mice placed in three different environmental temperatures (37, 71 and 98 F.), in an effort to determine in what manner external temperature influences mortality. The method of

6. Bergman, H. C., and Prinzmetal, M.: The Prevention of Burn Shock and the Reduction of Inflammatory Edema with Liver Extract, Morphine, Pentobarbital and Ethanol, to be published.

determining bleeding volume has been previously described.³ Briefly, it consists in removing the heart of etherized animals and mopping up the blood in the thorax with a weighed cotton pledget until the return flow of blood has ceased. This procedure requires about two to four minutes. It can be seen in chart 2 that a sharp reduction occurs in bleeding volume of burned animals subjected to a hot environment (98 F.) as compared with that of animals subjected to ordinary room temperature (71 F.). We were somewhat surprised to observe that in spite of the increased mortality of burned mice subjected to cold (37 F.) over that of burned mice at ordinary room temperature, the bleeding volumes of mice in the cold environment were reduced less than the bleeding volumes of mice at ordinary room temperature. It is reasonable to suppose that the increased mortality in the hotter environments can be attributed to the further reduction in effective circulation, with subsequent accentuation of the shock. But the increased mortality in cold environments cannot be attributed to this physiologic change. Efforts to find the possible cause of this increased mortality will be presented later.

EXPERIMENT 3.—Effect of environmental temperature on the toxic factor and capillary atony.

The amount of blood remaining in an organ after exsanguination of a shocked animal measures the degree of capillary atony which is caused by the toxic factor.² The amount of blood retained in the kidneys and livers was determined on three groups of burned mice at external temperatures of 37, 71 and 98 F. and on an equivalent group of nonburned mice. The hemoglobin content of the organs was estimated colorimetrically after extraction of the macerated tissues with 20 per cent urea solution with frequent shaking for twenty-four hours at ordinary room temperature; 10 cc. of urea solution was taken for each gram of tissue. Values for hemoglobin obtained by this method are only semi-quantitative, as indicated by work now in progress in our laboratory. The amount of hemoglobin retained after exsanguination in the kidneys and livers of burned mice kept at 37, 71 and 98 F. for three and one-half to four and one-half hours as compared with that retained by nonburned exsanguinated mice is shown in chart 3. It can be seen that there is an increased amount of hemoglobin in the organs of shocked animals in comparison with those of control animals, confirming our previous observations.² It can also be seen that the degree of capillary

atony, as measured by the hemoglobin content, is further increased when animals are kept at the hot environmental temperature. In the cold, on the other hand, there is a decrease in the degree of visceral congestion as compared with the congestion at ordinary room temperature.

EXPERIMENT 4.—Effect of environmental temperature on local fluid loss.

One hindlimb of 78 etherized mice was scalded at 65 C. (149 F.) for ten seconds. The animals were divided into three groups of 26 animals each and placed in environmental temperatures of 37, 71 and 98 F. respectively. The mice were killed three and one-half to four and one-half hours later by exsanguination under ether anesthesia. The amounts of local fluid loss and bleeding volumes

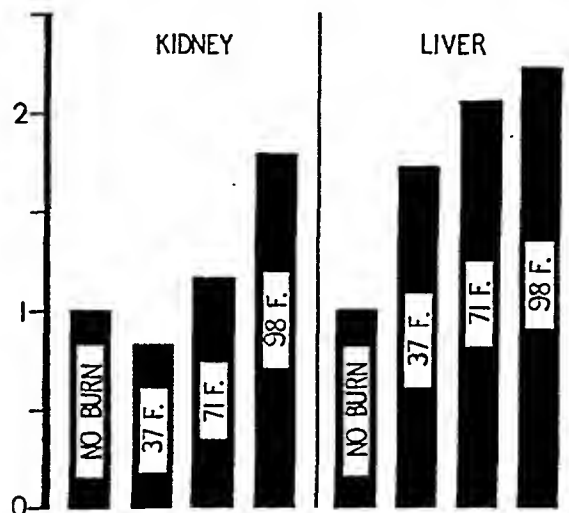


Chart 3.—Effect of environmental temperature on the degree of congestion in the kidneys and livers of burned mice. The results illustrated were obtained on the same mice for which data are presented in chart 2, equal masses of tissue being compared. Less hemoglobin was retained after exsanguination in the kidneys and livers of burned mice kept at 37 F. than at 71 F. More hemoglobin appeared after exsanguination in the kidneys and livers of burned mice kept at 98 F. than at 71 F. The latter results show a further increase in capillary atony in shocked mice exposed to a high external temperature. The numbers at the left indicate hemoglobin retention.

were determined. The method for estimating the degree of local fluid loss has been presented elsewhere.⁷ This is a modification of Blalock's bisection method.⁸ It can be seen from the table

7. Prinzmetal, M.; Bergman, H. C., and Hechter, O.: A Demonstration of Two Types of Burn Shock, *Surgery* 16:906-913, 1944.

8. Blalock, A.: Experimental Shock: VII. The Importance of the Local Loss of Fluid in the Production of Low Blood Pressure After Burns, *Arch. Surg.* 22: 610-616 (April) 1931.

that no significant difference in the degree of local fluid loss occurred in the environmental temperatures studied but the same relative changes in toxic factor and bleeding volume occurred after a burn involving 90 per cent of

and mice, burns at 100 C. (212 F.) for twenty seconds produce little or no local fluid loss and death is due entirely or almost entirely to the toxic factor. Burns at 65 C. for ten seconds, on the other hand, produce appreciable local fluid loss, which, together with the capillary toxic factor, causes a reduction in effective circulation. We are now attempting to determine whether these factors are operative in human injuries.

In connection with the present problem, it was felt important to know whether the factor of environmental temperatures which influence the mortality of mice with burns producing local fluid loss was likewise operative in mice with burns without local fluid loss. Toxic burn shock was produced in 60 etherized mice by scalding both hindlimbs at 100 C. for twenty seconds. The animals were divided into three groups of 20 mice each and placed in environmental temperatures of 37.4, 68.0 and 100.4 F. respectively. These groups were compared with equal numbers of mice scalded up to the head at 65 C. for ten seconds and placed in these various environmental temperatures at the same time. It can be seen in chart 4 that the general character of

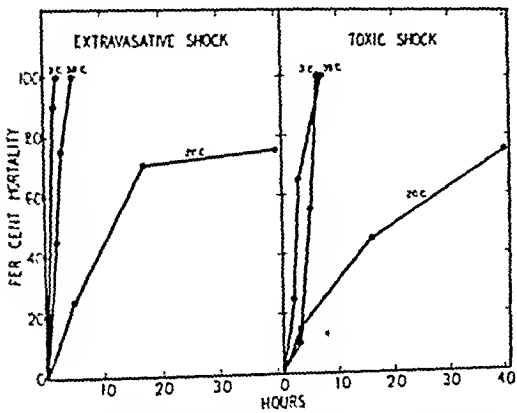


Chart 4.—Comparative effect of environmental temperature on extravasative and toxic shock. Each curve represents the response of 20 burned mice kept at the indicated temperature. Extravasative shock was produced by burning etherized mice up to the head at 65 C. for ten seconds. Toxic shock was produced by burning both hindlimbs at 100 C. for twenty seconds. In general the responses to the two procedures were similar.

Effect of Environmental Temperature on Etherized Mice with One Hindleg Scalded at 65 C. for Ten Seconds; Data Obtained Three and One-Half to Four and One-Half Hours After Trauma

Seconds; Data Obtained Three and One-half Hours After Burn											
Environment Temperature	No. of Mice	Local Fluid Loss (Per Cent Body Weight)				Bleeding Volume (Per Cent Body Weight)			Hemoglobin Retention (Ratio of Treated to Nontreated)		
		SD *	SE †	SR ‡		SD	SE	SR	Liver	Kidney	
37 F.	26	3.94	1.15	0.23	2.6	4.51	0.73	0.14	2.0	0.57	1.08
71 F.	26	4.82	1.20	0.24	...	4.08	0.60	0.16	...	1.15	1.09
98 F.	26	4.13	0.92	0.18	2.3	3.55	0.56	0.17	1.5	1.29	1.25
No burn	{ 12	0.59§	0.25	0.07	...	5.63	0.45	0.07	...	1.00	1.00
	{ 37						

* Standard deviation of a single observation.
† Standard error of the mean.
‡ Significance ratio, compared to 71 F.
§ The percentage difference in quadrant weight of 12 nonburned animals.

the body surface (charts 2 and 3). It must be realized that the entire animal was placed at these temperatures, and it is possible that if the burned area alone had been subjected to heat or cold the degree of local fluid loss might have been influenced.⁹

EXPERIMENT 5.—Effect of environmental temperature on extravasative and toxic shock.

It has been previously shown that animals may die in shock with or without local fluid loss, depending on the character of the burn.⁷ In rats

the time-mortality curves is the same in both types of burn. This experiment presents additional evidence that the deleterious effect of environmental temperature is not due to an effect on local fluid loss, since, as shown in this experiment, a similar effect on mortality occurs irrespective of local fluid loss.

COMMENT

An optimal temperature range for survival of shocked mice has been found to be 65 to 71 F. Small changes in temperature above or below this range cause a striking increase in mortality. It would appear to be of greatest importance to determine whether this general situation holds

9. Allen, F. M.: Resistance of Peripheral Tissues to Asphyxia at Various Temperatures, Surg., Gynec. & Obst. 67:746-751, 1938.

true for human beings. It has been suggested that this information could be obtained by making similar observations on anthropoid apes.¹⁰ The difficulties involved in such an attempt become apparent when one considers that in our first experiment it was necessary to use 400 animals to find the optimal temperature range. A priori, it would seem that environmental temperature might have less effect on human beings than on small laboratory animals during equal periods of exposure because of the larger mass involved. However, since it has been shown that environmental temperature influences the mortality of shock with many sorts of animals (dogs, rabbits, guinea pigs, rats and mice), it would seem reasonable to expect similar effects in persons. There is no evidence at present which suggests that the optimal temperature range for lowest mortality is different for human beings, and until contrary evidence is obtained it would seem advisable to accept these data as applicable. Operating rooms are often overheated in the winter, and facilities for air conditioning in summer are not always available. Likewise, it has been reported that many of the military operating rooms in the tropics are not air conditioned. In view of our observations, it is easy to see how injury resulting from long traumatizing surgical procedures might in such circumstances be aggravated, and the mortality attributed to so-called surgical shock would be greatly increased. After severe surgical procedures the patient should be placed in a cool room, at 65 to 71 F., until the possibility of further shock has passed. The same principle should apply to the management of other types of trauma which are so frequent in wartime. One exception to this rule should be noted as applying to the treatment of a severely chilled subject, in which case, as observed by Cannon,¹¹ the temporary application of heat often causes a good restoration of pulse, blood pressure and appearance.

All experiments on the effect of environmental temperature, including our own, have been done on animals without infections and spontaneous fever. It appears possible that these data may not apply in the presence of fever.

The deleterious effect of a hot environment on shock can be adequately explained by the

occurrence of a further decrease in blood volume and an increase in capillary atony and visceral congestion, which becomes demonstrable after exsanguination. It is possible that the increased capillary congestion is due to an increased production of the toxic products in the burned area. Heat increases metabolic activity. If a toxic product is a result of a chemical reaction following a burn, then increased amounts should be formed in a warm environment. One could assume that heat increases the blood flow to the burned area, causing greater absorption of the toxic materials. However, although the blood flow to a normal part is greatly increased by heat,¹² it has yet to be shown that this is true for inflamed areas.

The influences of cold on mortality is more difficult to explain. The lessened reduction of bleeding volume and the decreased capillary congestion are compatible with the hypothesis that a lesser concentration of the toxic substance is present in the circulating blood either because less is formed or because less is absorbed. Nevertheless, in spite of this apparent beneficial effect, there is an increased mortality. Since the increased mortality is not due to any known physiologic hemodynamic alteration, it must be due to a yet unknown change. In a few preliminary experiments, we have found that the administration of adrenal cortex extract or solution of dextrose did not influence the increased mortality in a cold environment. Thus, it is unlikely that adrenal exhaustion or hypoglycemia is the cause of the increased mortality. Others¹³ have found that the body temperature of animals subjected to cold is noticeably reduced, an observation which we readily confirmed in mice. Crismon^{13a} has demonstrated that death from hypothermia in normal rats is due to circulatory and respiratory failure. It would seem likely that temperature regulation is impaired in shocked animals because of the inadequate circulation and the reduced ability to compensate in other ways, such as by vigorous shivering. The deleterious effects of cold should

12. Prinzmetal, M., and Wilson, C.: The Nature of the Peripheral Resistance in Arterial Hypertension with Special Reference to the Vasomotor System, *J. Clin. Investigation* **15**:63-83, 1936.

13. (a) Crismon, J. M.: Effect of Hypothermia on the Heart Rate, the Arterial Pressure and the Electrocardiogram of the Rat, *Arch. Int. Med.* **74**:235-243 (Oct.) 1944. (b) Blalock and Mason.¹³

10. Cooling in Shock, editorial, *J. A. M. A.* **121**:432-433 (Feb. 6) 1943.

11. Cannon, W. B.: Personal communication to the authors.

be considered if one attempts to treat the entire body by refrigeration, as recommended for therapeutic use in a variety of ailments.¹⁴

CONCLUSIONS

1. The optimal environmental temperature range for highest survival of mice in burn shock was found to be 65 to 71 F.

2. In a hot environment, the increased mortality in shock is due to a further decrease in

the effective circulation and an increase in capillary congestion caused by the toxic factor.

3. In shocked mice kept in a cold environment, an increased bleeding volume and a reduced degree of capillary atony were found when compared with values obtained in an environment with ordinary room temperature. The cause of the increased mortality in a cold environment is as yet unknown.

4. Environmental temperatures of 37, 71 and 98 F. had no significant effect on local fluid loss following burns.

14. Smith, L. W.: The Use of Cold in Medicine, *Ann. Int. Med.* 17:618-636, 1942.

BLOOD IODINE STUDIES

VI. AN ANALYSIS OF THE BLOOD IODINE IN THYROID DISEASE

GEORGE M. CURTIS, M.D., AND M. BEEN FERTMAN, M.A.
COLUMBUS, OHIO

A principal consideration in this series of studies is the relation of the blood iodine level to the basal metabolic rate in various physiologic and pathologic states.

Within recent years there have been an abundance of investigations directed toward the understanding of the nature of blood iodine, and many features have thus been revealed. But as yet its essential composition and the exact relation it bears to the thyroid hormone is unknown. Its clinical value, notwithstanding, has become increasingly apparent, particularly for patients with thyroid disease, for whom the basal metabolic rate alone is inadequate as a diagnostic measure. Its theoretic value in disclosing causal relationships in certain diseases may prove of even greater significance. For these reasons, we have made a comparative analysis of the blood iodine, basal metabolic rate and certain other factors in 138 different clinical conditions in a total of 818 persons. Our earlier blood iodine values, from 1932 to 1936, were determined by the dry ash technic,¹ and the remainder, from 1936 to date, by the chromium trioxide method.²

VALUE OF BLOOD IODINE DETERMINATIONS

There are persons who maintain that blood iodine determinations are of questionable clinical value. They feel that the method is too cumbersome to warrant its use, particularly in view of the availability of basal metabolic rate determinations, which they consider not only more practical but sufficiently inclusive, as a laboratory aid in the recognition of changes in thyroid function.

From the Department of Surgical Research, the Ohio State University.

Aided by a grant from the Comly Fund for Research of the Ohio State University.

1. Davis, C. B., and Curtis, G. M.: Blood Iodine Studies: I. The Quantitative Determination of the Iodine Content of Blood, *J. Lab. & Clin. Med.* **18**:24, 1932. Phillips, F. J., and Curtis, G. M.: Blood Iodine Studies: IV. The Clinical Determination of Iodine in Blood, Urine and Feces, *Am. J. Clin. Path.* **4**:346, 1934.

2. Matthews, N. L.; Curtis, G. M., and Brode, W. R.: Determination of Iodine in Biological Materials: Refinements of the Chromium Trioxide Oxidation Method, *Indust. & Engin. Chem.* **10**:612, 1938.

What they fail to see, however, is that the two methods should be used side by side, each as a supplement to the other. Nor are analyses of blood iodine now especially cumbersome or lacking in precision.

The blood iodine, and specifically its protein-bound fraction, is an index of the circulating thyroid hormone.³ As shown by tolerance curves, it is regulated essentially by the functional activity of the thyroid gland.^{3a} This is the principal basis for its importance in clinical as well as in experimental studies.

The behavior of the blood iodine, particularly of its organic, or protein-bound, fraction, may prove to be of diagnostic significance in instances in which it is difficult or even impossible to obtain a reliable determination of the basal metabolic rate; also, in the differentiation of hyperthyroidism from other simulating conditions, in which the basal metabolic rate is likewise elevated, as, for example, in patients with hypertension or with cardiac decompensation. Further, it is of value in distinguishing goiter with hyperthyroidism clinically from goiter without hyperthyroidism, in which the basal metabolic rate may be otherwise increased.

Perkin and Cattell have presented convincing evidence that the amount of iodine in the blood may be a more reliable criterion than the basal metabolic rate in the differential diagnosis of borderline hyperthyroidism, so important a decision, especially in the consideration of therapy.⁴ In a study of 235 patients with borderline hyperthyroidism under carefully controlled conditions, they found that despite a generally elevated basal metabolic rate the blood iodine level was not significantly increased in the majority of persons for

3. (a) Salter, W. T.: *The Endocrine Function of Iodine*, Cambridge, Mass., Harvard University Press, 1940. (b) Salter, W. T., and Bassett, A. M.: *A Physiological Interpretation of Blood Iodine Fractions in Terms of Thyroid Function (in One Hundred Cases)*, *Tr. A. Am. Physicians* **56**:77, 1941. (c) Man, E. B.; Smirnow, A. E.; Gildea, E. F., and Peters, J. P.: *Serum Iodine Fractions in Hyperthyroidism*, *J. Clin. Investigation* **21**:773, 1942.

4. Perkin, H. J., and Cattell, R. B.: *The Value of Blood Iodine Estimations in the Diagnosis of Borderline Hyperthyroidism*, *West. J. Surg.* **48**:59, 1940.

whom a tentative diagnosis of mild hyperthyroidism was unsupported by the clinical observations or in most of those patients with nodular or exophthalmic goiter who subsequently did not benefit by subtotal thyroidectomy. On the other hand, both the basal metabolic rate and the blood iodine level for the most part were elevated preoperatively and declined postoperatively in those who improved clinically after an adequate thyroidectomy.

From a further investigation of 256 patients with exophthalmic goiter, Perkin and Hurxthal concluded that estimations of the blood iodine level taken at stated intervals offer a means whereby predisposition to recurrence or persistence of clinical hyperthyroidism can be predicted.⁵ Moreover, the level of the blood iodine may be used as an index for determining the correct amount of thyroid tissue to remove,⁶ thus diminishing materially the postoperative

with total intrathoracic goiter or with other abundant thyroid tissue, which may be otherwise overlooked. Further, its estimation, as well as that of the urinary output of iodine, will furnish useful evidence in the detection of temporarily induced hyperthyroidism from secretly ingested desiccated thyroid.⁷

The blood iodine appears to be a more specific and consequently more reliable, measure of thyroid overactivity than the serum cholesterol. Riggs and his co-workers found only 16 of 2 hyperthyroid patients with serum cholesterol values less than the minimum of the normal range, which is about 150 mg per hundred cubic centimeters.⁸

THE BLOOD IODINE IN TOXIC AND IN NONTOKIC GOITER

The clinical groups of thyroid diseases listed in table 1 were collected according to their clinical

TABLE 1.—The Average Blood Iodine Level in Various Thyroid Diseases, Together with the Standard Error and a Comparison with the Basal Metabolic Rate

Clinical Diagnosis	Blood Iodine, Micrograms per 100 Cc.				Basal Metabolic Rate, %	
	Method					
	Chromium Trioxide	Dry Ash				
	No. Cases	Mean \pm S. E.	No. Cases	Mean \pm S. E.	No. Cases	Mean \pm S. E.
Normal.....	39	4.2 \pm 0.2	16	11.9 \pm 0.5	45	-5 \pm 1
Hypothyroidism.....	69	3.6 \pm 0.1	13	11.9 \pm 1.2	77	-16 \pm 1†
Nontoxic diffuse colloid goiter.....	9	4.4 \pm 0.3	5	10.3 \pm 2.1	14	-7 \pm 2
Nontoxic nodular goiter.....	44	3.9 \pm 0.2	20	11.5 \pm 2.0	72	+1 \pm 1†
Toxic nodular goiter.....	29	7.9 \pm 0.5†	25	15.8 \pm 1.1*	54	+28 \pm 2†
Toxic diffuse colloid goiter.....	3	6.4 \pm 0.7†	3	15.7 \pm 0.8†	6	+20 \pm 9†
Toxic mixed goiter.....	4	7.2 \pm 1.1†	4	+26 \pm 5†
Exophthalmic goiter.....	41	9.3 \pm 0.6†	34	17.6 \pm 1.0*	73	+39 \pm 3†
Carcinoma of the thyroid.....	9	4.8 \pm 0.7	3	16.6 \pm 2.7*	11	+16 \pm 3†
Chronic thyroiditis.....	3	5.2 \pm 0.9	3	-12 \pm 3

* Significantly different from the normal mean; chances are better than 20 to 1 that this difference is not due to chance alone.

† Highly significantly different from the normal mean; chances are better than 100 to 1 that this difference is not due to chance alone.

complications of hypothyroidism or recurrent hyperthyroidism.

Similarly, Salter and Bassett found that the clinical diagnosis is better correlated with the plasma protein-bound iodine than with the basal metabolic rate.^{3b} On the basis of his work, Salter concluded that Graves' disease may exist without physiologic hyperthyroidism.^{3a,b}

The determination of the blood iodine may also prove of value for patients with ovarian struma,

5. Perkin, H. J., and Hurxthal, L. M.: The Blood Iodine Level Before and After Subtotal Thyroidectomy for Hyperthyroidism, *New England J. Med.* 215:698, 1936.

6. Cattell, R. B., and Perkin, H. J.: Recurrent Hyperthyroidism: The Likelihood of Recurrence in Relation to the Preoperative Blood Iodine Level, *West. J. Surg.* 47:55, 1939. Perkin, H. J., and Cattell, R. B.: Blood Iodine Levels Related to the Recurrence of Hyperthyroidism, *Surg., Gynec. & Obst.* 68:744, 1939. Perkin and Hurxthal.⁵

cal diagnoses. From this table it may be seen that the average blood iodine concentration is significantly elevated in each form of toxic goiter and that with this increase is associated an elevation of the basal metabolic rate. On the other hand, the average blood iodine in patients with nontoxic goiter does not exceed normal, although it may be accompanied by a moderately increased basal metabolic rate.⁹

7. Perkin, H. J.; McFarland, M. D., and Hurxthal, L. M.: Temporarily Induced Thyrotoxicosis from Secretly Ingested Desiccated Thyroid: Its Detection by Blood and Urinary Iodine Estimations, *Lahey Clin. Bull.* 2:186, 1941.

8. Riggs, D. S.; Gildea, E. F.; Man, E. B., and Peters, J. P.: Blood Iodine in Patients with Thyroid Disease, *J. Clin. Investigation* 20:345, 1941.

9. Curtis, G. M., and Fertman, M. B.: Blood Iodine Studies: VII. The Basal Metabolic Rate and Its Relationship to the Blood Iodine in Thyroid Disease, unpublished data.

Other investigations have likewise revealed the absence of hyperthyroidism in patients with nontoxic goiter. The blood iodine¹⁰ as well as the urinary excretion of iodine^{10a,b} is within normal range, while the basal metabolic rate may be normal or even somewhat increased.^{10b} Moreover, the iodine balance appears within normal physiologic limits.¹¹ Perkin and his associates found the average blood iodine level in 111 patients with nontoxic nodular goiter to be identical with that in 112 normal persons.^{10c} Turner and his co-workers reported the blood iodine normal in 4 of 5 patients with nontoxic nodular goiter and low in the fifth.¹² Not only the total blood iodine but also the acetone-water-insoluble fraction is diminished, correlated with the varying degrees of exhaustion, atrophy and fibrous replacement shown by microscopic sections of the surgically removed gland.¹³ The amount of circulating blood iodine in this disease

Contrasted with this picture of the blood iodine in nontoxic goiter, one finds in any form of toxic goiter a significant increase not only in the average blood iodine but also in the variation of the individual blood iodine values among the different patients. Thus in table 2 the values are arbitrarily divided into five groups, based on normal 1 s.d. and 2 s.d. (one and two times the standard deviation) limits. The per cent of blood iodine values of the combined dry ash and chromium trioxide studies which fall within each of these groups is shown. From this table it becomes clear that the average blood iodine level in toxic nodular goiter and in exophthalmic goiter differs significantly from the normal.

Approximately three quarters of the levels in exophthalmic goiter and nearly that many of the levels in toxic nodular goiter fall above the normal ± 1 s.d. limit. Over half the patients with any form of toxic goiter had blood iodine values

TABLE 2.—Distribution of Individual Blood Iodine Values in the Normal ± 1 S.D.* and 2 S.D. Limits

Normal average blood iodine ± 2 the standard deviation = 4.2 ± 1.2 micrograms per hundred cubic centimeters by the chromium trioxide method² and 11.9 ± 3.2 micrograms per hundred cubic centimeters by the dry ash method.¹

Clinical Diagnosis	Cases, No.	Below -2 S. D., %	-2 S. D. to -1 S. D., %	-1 S. D. to Average, %	Average to +1 S. D., %	+1 S. D. to +2 S. D., %	Above +2 S. D., %
I. Normal.....	55	0	13	44	24	16	3
II. Nontoxic nodular goiter.....	74	1	18	42	24	8	7
III. Toxic nodular goiter.....	57	0	5	11	23	16	45
IV. Exophthalmic goiter.....	75	0	2	9	11	15	63
V. All toxic goiters, including III, IV, mixed and diffuse colloid.....	142	1	5	9	16	15	54

* 1 S. D. indicates 1 \times the standard deviation; 2 S. D. indicates 2 \times the standard deviation, etc.

appears to be dependent on the amount of gland involved in the pathologic changes as well as on the degree of involution or degeneration within the nodules.

10. (a) Curtis, G. M.; Davis, C. B., and Phillips, F. J.: Significance of the Iodine Content of Human Blood, *J. A. M. A.* **101**:901 (Sept. 16) 1933. (b) Elmer, A. W., and Scheps, M.: The Iodine Content of the Blood and of Urine and the Basal Metabolic Rate: Their Value in the Diagnosis of the Function of the Thyroid Gland, *Acta med. Scandinav.* **82**:126, 1934. (c) Perkin, H. J.; Lahey, F. H., and Cattell, R. B.: Blood Iodine Studies in Relation to Thyroid Disease: Basic Concept of the Relation of Iodine to the Thyroid Gland: Iodine Tolerance Test, *New England J. Med.* **214**:45, 1936. (d) Riggs, Gildea, Man and Peters.⁵

11. Puppel, I. D., and Curtis, G. M.: The Iodine Balance in Nodular Goiter, *J. Clin. Investigation* **17**: 729, 1938.

12. Turner, K. B.; DeLamater, A., and Province, W. D.: Observations on the Blood Iodine: I. The Blood Iodine in Health, in Thyroid and Cardioresenal Disease and in Leukemia, *J. Clin. Investigation* **19**:515, 1940.

13. Davison, R. A.; Zollinger, R. W.; Curtis, G. M.; Surington, C. T., and Riley, E. L.: The Fractionation of the Blood Iodine: II, unpublished data.

exceeding the normal ± 2 s.d. limit. Of these values 52 per cent were as much as from two to five times the normal mean, whereas the highest value obtained for normal persons did not attain twice the mean.

While there appears to be a difference in the distribution of the blood iodine values in these groups of toxic nodular and exophthalmic goiter above the normal ± 2 s.d. limit (table 2), yet it will be seen from table 3 that the blood iodine concentration in toxic nodular goiter can attain as high a level as in exophthalmic goiter. Also, it is to be noted that the average of all the blood iodine values above the normal ± 2 s.d. limit for each of these groups is almost identical.

The mean blood iodine level determined by the chromium trioxide technic was 7.9 micrograms per hundred cubic centimeters for 29 patients with toxic nodular goiter and 9.3 micrograms for 41 patients with exophthalmic goiter. By the dry ash method, the corresponding values for 28 patients with toxic nodular goiter and 34 with exophthalmic goiter were 15.8 and 17.6

micrograms, respectively (table 1). Nevertheless, by statistical tests we were unable to prove that these values or those of any two of the groups of toxic goiter included in this study differ significantly from each other; the variation of the blood iodine levels among the individual patients was greater than the difference between the means of each group. In view of the difference between the average basal metabolic rate in toxic nodular goiter and in exophthalmic goiter⁹ and in view of an apparent dissimilarity in the iodine balance,¹¹ some difference in the blood iodine would be expected. This difference might be evidenced quantitatively in the relative proportions of the fractions of blood iodine, if not in the total blood iodine concentrations. With more data it may be possible to demonstrate statistically such quantitative differences. On the other hand, a difference in blood iodine in these two diseases may be more qualitative than quantitative.

Investigators concur that for the most part the blood iodine concentration is elevated in hyperthyroidism.¹⁴ R. G. Turner reported that 10 of 15 patients with this disease had elevated blood iodine values whereas the values of the other three were normal.^{14c} Perkin and his co-workers¹⁵ and K. B. Turner¹² have likewise found approximately 30 per cent of their hyperthyroid patients to have a normal blood iodine. Riggs and his associates, however, observed an increased blood iodine in this disease of from two to six times the highest normal level, with no instances of normal values.¹⁶

Salter and Bassett reported that the plasma protein-bound iodine increases with the degree of thyroid activity while the inorganic ionized iodine in the protein-free plasma filtrate remains relatively constant.^{3b} Man, Smirnow and Gildea^{3c} observed the total as well as the precipitable

serum iodine to be distinctly above the normal range in 15 hyperthyroid patients.

High blood iodine values have also been noted in children with exophthalmic goiter¹⁷ and in patients with induced hyperthyroidism.^{12a} The increased blood iodine in exophthalmic goiter rises still higher with administration of iodine, yet the consequent increased storage of iodine in the thyroid gland results ultimately in a diminution of the circulating thyroid hormone.^{14b} On initiation of iodine medication to patients with exophthalmic goiter, the inorganic iodine of the blood increases rapidly, yet the organic fraction falls at once,¹⁸ apparently owing to a decrease in thyroid secretion.¹⁹ Bülmann²⁰ and Man and her associates^{3c} report a drop in the plasma protein-bound iodine in hyperthyroidism with iodine medication. On the other

TABLE 3.—Extent of Elevation of the Blood Iodine Levels, Values Above the Normal ± 2 S.D.* Limit, Their Average and Maximum

Clinical Diagnosis	Method of Blood Iodine Determination			
	Chromium Trioxide		Dry Ash	
	Cases, No.	Value, Micrograms per 100 Cc. Average Highest	Cases, No.	Value, Micrograms per 100 Cc. Average Highest
Normal.....	1	(7.4) 7.4	1	(10.0) 10.0
Toxic nodular goiter.....	17	10.0 21.5	9	25.1 25.5
Exophthalmic goiter.....	33	10.4 18.4	14	23.2 32.3

* $2 \times$ the normal standard deviation.

hand, there appears to be a relative increase in the organic blood iodine in patients with non-toxic goiter receiving iodine.²¹

17. Curtis, G. M.: Juvenile Thyrotoxicosis, *S. Clin. North America* 12:197, 1932. Curtis, Davis and Phillips.^{10a}

18. Holst, J.; Lunde, G.; Closs, J., and Pedersen, O. C.: Ueber den inneren Jodstoffwechsel bei primären Thyreotoxikosen (Primär-Basedow). *Klin. Wchnschr.* 7:2287, 1928. Holst, J., and Lunde, G.: Intermediate Iodine Metabolism During the Preoperative Treatment of Exophthalmic Goiter, *Am. J. Surg.* 7:39, 1929.

19. Lunde, G.; Closs, K., and Pedersen, O. C.: Untersuchungen über den Jodstoffwechsel: 111. Untersuchungen über den Blutjodspiegel bei der primären Thyreose, *Biochem. Ztschr.* 206:261, 1929. Sturm, A.: Beiträge zur Kenntnis des Jodstoffwechsels. V. Mitt. Stoffwechselstudien an den überlebenden Schilddrüsen: I. Der Jodstoffwechsel der überlebenden künstlich durchströmten Hundeschilddrüsen, *Ztschr. f. d. ges. exper. Med.* 74:514, 1930.

20. Bülmann, G.: Ueber den Blutjodspiegel: Seine Bestimmung und Seine Beziehung zum Grundumsatz besonders bei Myxoedem und Morbus Basedow, *Skandinav. Arch. f. Physiol.*, 1938, supp. 12, p. 1.

21. Perkin, H. J., and Hursthal, L. M.: The Fractionation of the Iodine of the Blood in Thyroid Disease, *J. Clin. Investigation* 18:733, 1939.

14. (a) Curtis, G. M., and Davis, C. B.: The Blood Iodine in Diseases of the Thyroid, *Proc. Inst. Med. Chicago* 8:14, 1931. (b) Curtis, G. M.: The Iodine Relationships of Thyroid Disease, *Surg., Gynec. & Obst.* 62:365, 1936. (c) Turner, R. G.: Iodine Content of Certain Pathological Bloods in a Goiterous Region, *Proc. Soc. Exper. Biol. & Med.* 29:1294, 1932. (d) McCulloch, D. R.: Studies in Blood Iodine by the Use of a New Chemical Method, *Cleveland Clin. Quart.* 2:15, 1935. (e) Man, Smirnow, Gildea and Peters.^{3c} (f) Riggs, Gildea, Man and Peters.⁸ (g) Curtis, Davis and Phillips.^{10a} (h) Elmer and Scheps.^{10b} (i) Turner, DeLamater and Province.¹²

15. (a) Perkin, H. J., and Lahey, F. H.: The Level of Iodine in the Blood, *Arch. Int. Med.* 65:882 (May) 1940. (b) Perkin, Lahey and Cattell.^{10c}

16. Riggs, D. S.; Gildea, E. F., and Man, E. B.: The Clinical Interpretation of Blood Iodine Levels, *Connecticut M. J.* 5:209, 1941. Riggs, Gildea, Man and Peters.⁸

BLOOD IODINE AND DURATION OF THYROID DISORDER

Perkin and Lahey reported that the blood iodine in hyperthyroidism is correlated with the exhaustion of the patient's store of body iodine when the disease has existed a sufficiently long time.^{15a} They found that the blood iodine is usually elevated when the hyperthyroid symptoms have been present for less than nine months.²² On the other hand, the blood iodine is generally within normal range in patients exhibiting untreated symptoms for one year or more. Further, if the symptoms of clinical hyperthyroidism are allowed to persist untreated for four to five years, the blood iodine level is not only normal but in most cases uninfluenced by thyroidectomy.²²

Contrary to these observations are those of Riggs and his associates, who could find no relationship between the level of the blood iodine and the duration of symptoms in hyperthyroidism. The average blood iodine of 18 hyperthyroid patients with symptoms present less than one year was 10.5 micrograms per hundred cubic centimeters, and of 13 with symptoms existing at least one year the average was 10.9 micrograms.⁵

We are unable to find any significant correlation between the blood iodine level and the duration of symptoms in any of the thyroid diseases considered in this report. Nor is there any significant correlation between either the blood iodine or the basal metabolic rate alone and the total duration of either toxic nodular or exophthalmic goiter. On the other hand, we did obtain significant positive multiple correlation coefficients, demonstrating a probable association, between the blood iodine and the combined variables of basal metabolic rate and duration of toxic symptoms in hyperthyroidism or of goiter in nontoxic nodular goiter.⁹ However, the association indicates, if anything, that the blood iodine increases, rather than decreases, with an increase in some combination of the other two factors.

BLOOD IODINE IN HYPOTHYROIDISM

In a series of 66 hypothyroid patients whose blood iodine was determined by the chromium trioxide method and in 13 other hypothyroid patients, whose blood iodine was determined by the dry ash method, the average blood iodine values found were 3.6 and 11.8 micrograms per hundred cubic centimeters, respectively. These

values do not differ significantly from the corresponding normal values of 4.2 and 11.9 micrograms per hundred cubic centimeters, even though the average basal metabolic rate of these patients is definitely reduced (table 1). While no history of iodine medication was obtained,²³ it is likely that some of these patients had at one time a form of supplementary iodine. Also, possibly contributory to our negative finding may be the occurrence of a somewhat lowered blood iodine of the normal persons living in this goitrous area.

In general, the blood iodine in hypothyroidism as well as in cretinism is admitted to be lower than normal.²⁴ The blood iodine of cretins has been reported to be 36 per cent ^{24a} and even decreased as much as 50 or 70 per cent ^{24b}, while the blood iodine in hypothyroidism may be as much as 25 per cent lower than normal.^{24c} K. B. Turner and his associates found low and low normal blood iodine levels in 5 patients with hypothyroidism,¹² and R. G. Turner observed normal blood iodine values in 4 patients with this disease.^{14c} However, Riggs and his co-workers could find no overlap in the lowered blood iodine of 7 myxedematous patients with that of 26 euthyroid persons.⁵ Other investigators have reported that the blood iodine is decreased in hypothyroidism apparently in proportion to the degree of underfunction.^{24f} Yet while the decrease in the blood iodine in hypothyroidism ordinarily corresponds to the lowering of the basal metabolic rate, in atypical forms of this disease, Elmer and Scheps reported, the decrease in the blood iodine is not commensurate with the drop in basal metabolic rate.^{10b} This may also explain the disproportionately greater reduction of the basal metabolic rate than of the blood iodine which can occur in post-operative myxedema.^{24a}

The application of the principle of fractionation of the blood iodine eliminates the incongruous

23. Most of these patients were from the outpatient clinic, and in general their histories did not include any story of possible supplementary iodine.

24. (a) Curtis, G. M.; Cole, V. V., and Phillips, F. J.: *The Blood Iodine in Thyroid Disease*, West. J. Surg. **42**:435, 1934. (b) de Quervain, F., and Smith, W. E.: *The Iodine Content of Blood in Ordinary Goitres and in Cretinism*, *Endocrinology* **12**:177, 1928. (c) Kisch, F.: *Zur Klinik atypischer Blutjodwerte*, *Klin. Wchnschr.* **15**:342, 1935. (d) Schwenk, W.: *Untersuchungen über den Blutjodgehalt im Kindesalter*, *Monatschr. f. Kinderh.* **79**:349, 1939. (e) McCullagh, E. P., and McCullagh, D. R.: *Clinical Experiences in the Use of Determinations of Blood Iodine*, *Arch. Int. Med.* **57**:1051 (June) 1935. (f) de Goës, P., and de Souza Luz, H.: *A iodemia nos estados distireoides*, *Hospital, Rio de Janeiro* **17**:677, 1940. (g) Riggs, Gildea, Man and Peters. (h) Curtis, Davis and Phillips.^{10a} (i) Elmer and Scheps.^{10b} (j) Turner, DeLamater and Province.¹² (k) Curtis and Davis.^{14a}

22. Perkin, H. J., and Lahey, F. H.: *Exophthalmic Goiter: Relationship Between the Blood Iodine Level and the Duration of Symptoms in 305 Cases of Exophthalmic Goiter*, *Arch. Int. Med.* **61**:875 (June) 1938.

picture of a reduced basal metabolic rate co-existing with normal blood iodine in hypothyroidism; this occurs mainly because the portion of the blood iodine containing the iodine of nutrition and of broken-down thyroid hormone is thus separated from the fraction which presumably contains the thyroid hormone or a derivative thereof. The organic blood iodine, whether it is the alcohol-insoluble²¹ or the acetone-water-insoluble fraction²⁵ or the protein-bound plasma iodine,^{2a} is consistently low in patients with hypothyroidism.

BLOOD IODINE IN CARCINOMA OF THE THYROID

As will be discussed in a subsequent paper, no significant elevation of the blood iodine was noted in patients with nonthyroid carcinomas, a group which did not include any patients with malignant neoplasms of the liver.²⁶ However, the blood iodine in carcinoma of the thyroid may oc-

TABLE 4.—Comparison of Ranges and Averages of Blood Iodine Levels (Chromium Trioxide Method)

Clinical Diagnosis	No. of Cases	Range, Micrograms per 100 Cc.	Average, Micrograms per 100 Cc.
Normal.....	59	2.3 - 7.4	4.2
Carcinoma of the thyroid.....	9	2.2 - 7.5	4.5
Toxic nodular goiter.....	29	3.2 - 21.5	7.9 *
Exophthalmic goiter.....	41	3.6 - 18.4	9.3 *

* * Highly significantly greater than normal.

asionally be elevated. Such an elevation previously reported²⁷ was found in 3 patients, whose blood iodine was determined by the dry ash method (table 1). Two of the patients had both an increased blood iodine and an increased basal metabolic rate; in the third, a woman with goiter of forty years' duration, only the basal metabolic rate was elevated.

On the other hand, while the average basal metabolic rate was likewise significantly increased in 9 other patients with thyroid carcinoma, whose blood iodine was determined later by the chromium trioxide technic, the average blood iodine concentration found was 4.8 micrograms per hundred cubic centimeters, which does not differ significantly from the normal average of 4.2 micrograms (tables 1 and 4). Normal

blood iodine values were observed in patients who had had goiter over ten and twenty and for thirty years; yet the highest value, 7.8 micrograms per hundred cubic centimeters, was found in a patient whose goiter was also present for "many" years. A low normal blood iodine of 2.5 micrograms per hundred cubic centimeters was noteworthy in a patient with carcinoma occurring in an aberrant lateral thyroid.

In 3 other isolated determinations of the blood iodine in cases of carcinoma of the thyroid reported in the literature, the level of the blood iodine was found to be normal.²⁸ The basal metabolic rate observed in 2 of the cases was, as we have also noted in our series, elevated.^{24c}

It would consequently appear that the level of the blood iodine in carcinoma of the thyroid is more dependent on the nature of the thyroid gland in which the malignant growth arises than on the malignant growth itself. As we have mentioned, the average blood iodine in nontoxic goiter is also normal, even in the presence of an elevated basal metabolic rate. This is apparently likewise true in various forms of carcinoma.²⁶ Further, we were unable to find any correlation between the blood iodine and either the duration of the symptoms due to the carcinoma or the duration of a preceding goiter, when such was reported. Thus, we are unable to present any evidence of an association between the height of the blood iodine and the amount of degeneration taking place within the goiter. More data may, however, reveal such a correlation, and pathologic studies may indicate that the degree of degeneration, dependent on or possibly even independent of the time factor, may play an important role.

BLOOD IODINE IN THYROIDITIS

In 3 patients with chronic thyroiditis the average blood iodine determined by the chromium trioxide method was 5.2 micrograms per hundred cubic centimeters but was not significantly elevated. The values ranged from 3.4 to 6.4 micrograms per hundred cubic centimeters. On the other hand, K. B. Turner and his co-workers reported elevated blood iodine values in 2 patients with thyroiditis.¹² Riggs and his associates found a similarly high level of blood iodine in 1 patient with thyroiditis; there were no other symptoms or physical findings of hyperthyroidism.⁴

SUMMARY

1. Analyses of blood iodine in conjunction with the determination of the basal metabolic rate

28. Turner, DeLamater and Province.¹² McCullagh¹² and McCullagh.^{24c}

25. Davison, R. A.; Zollinger, R. W., and Curtis, G. M.: The Fractionation of the Blood Iodine: I. Findings in Patients with Normal Thyroid Function and with Hypothyroidism, *J. Lab. & Clin. Med.* 27:643, 1942.

26. Curtis, G. M., and Fertman, M. B.: Blood Iodine Studies: VIII. The Blood Iodine in Non-Thyroid Disease; IX. The Basal Metabolic Rate and Its Relationship to the Blood Iodine in Non-Thyroid Disease, unpublished data.

27. Curtis.^{24b} Curtis, Cole and Phillips.^{24a}

are of importance in the differential diagnosis of thyroid dysfunction.

2. The average blood iodine level was found to be significantly elevated in all forms of toxic goiter, and variations in the individual blood iodine values were likewise found to exceed those of normal persons. Associated with the increase in the blood iodine there occurred an elevated average basal metabolic rate.

In no two groups of toxic goiter, including the exophthalmic variety, was there found by statistical test any significant difference between the average blood iodine concentrations. However, some difference in the nature or quantity of the whole or fractionated blood iodine might be expected in exophthalmic goiter and should be further investigated.

It was noted that the blood iodine may rise as high in toxic nodular goiter as in exophthalmic goiter.

3. On the other hand, the average blood iodine level was not significantly elevated in nontoxic nodular goiter and in nontoxic diffuse colloid goiter. The average basal metabolic rate was significantly increased in nontoxic nodular goiter but averaged only — 7 per cent in diffuse nontoxic colloid goiter.

4. The average blood iodine in 79 patients with hypothyroidism was not significantly lower than that in normal persons from this goitrous region, although the average basal metabolic rate was definitely reduced. The value of the average blood iodine may have been influenced by pre-

vious iodine medication in certain instances, of which, however, there was no record. The importance of fractionation of the blood iodine, especially for such patients, is emphasized.

5. The average blood iodine in 9 patients with carcinoma of the thyroid, unlike that of a previous group of 3 similar patients, did not differ significantly from the normal, in spite of an elevated basal metabolic rate. There was no significant correlation between the blood iodine level and the duration of the symptoms due to the carcinoma or to those of goiter when such was recorded. It would appear that the level of the blood iodine in carcinoma of the thyroid is more dependent on the nature of the thyroid gland in which the malignant growth occurs than on the malignant growth itself.

6. In none of the thyroid disorders investigated was there found any significant linear correlation between the level of the blood iodine and the duration of symptoms or of goiter. However, that some association may exist was indicated by a significant positive multiple correlation coefficient of the blood iodine in relation to the basal metabolic rate and the duration of toxic symptoms in hyperthyroidism or of goiter in nontoxic nodular goiter. If anything, this relationship shows that the blood iodine increases rather than decreases with some combination of the other two factors.

7. In 3 patients with chronic thyroiditis, the average blood iodine was not significantly elevated.

EARLY AND LATE POSTOPERATIVE AMBULATION

A COMPARATIVE STUDY OF THREE HUNDRED AND THREE CASES

VINCENTE D'INGIANNI, M.D.

NEW ORLEANS

The exponents of early postoperative ambulation are becoming progressively more numerous, if one is to judge by the number of cases reported by individual authors. Zava¹ alone reported 6,000 cases. The literature surveyed in the course of this study presented no instance of reversion to the older modes of treatment once early ambulation had been tried.

Although propaganda for early ambulation has been under way, several writers have claimed to have "discovered" or "hit on" this manner of postoperative treatment independently. Zava noted that insane patients moved about frequently immediately after operation with no ill effects. Nelson² observed that children did well in spite of the fact that they were restless and active and that animals walked immediately after surgical treatment with no disruption of the wound. Leithauser³ and Nelson² independently observed that self ambulation not only caused no ill effects in children but resulted in benefit.

My own experience with this mode of treatment dates from the hospitalization of an 82 year old woman who had a cholecystectomy. Being specially anxious to prevent pneumonia, I instructed the nurses to have the patient sit in a wheel chair. This was accomplished after she took a few steps. Only some time later was it realized that the patient sat up on the second postoperative day. The results were good, and the evidence for and against early ambulation was examined. The objections appeared to be non-physiologic and empiric.

If persons are not to become ambulatory within the first day or two, why allow them to get up on the tenth day, when the sutures are weakest? If muscles are to be maintained in normal tone, why splint them? If circulation is increased by

muscular contraction, why slow it down by immobilization? If stasis promotes clotting, which predisposes to pulmonary embolism, why immobilize the patient? If early ambulation promotes healing, why not practice it?

With these thoughts in mind, I allowed all my patients to be out of bed immediately after operation, as early as the first day. In order to determine better the advantages and the disadvantages of this so-called radical change in postoperative treatment, a comparative study was made of 303 patients who were treated during the same period, 150 of whom received relatively conservative treatment and 153 of whom became ambulatory immediately after operation. This study was made possible through the cooperation of Dr. Christopher Bellone and Dr. Nicholas Tessitore.

Some facts which suggest that patients should be made ambulatory soon after operation are as follows:

1. Healing of wounds has become a lively topic of discussion and is closely associated with early ambulation. It has been shown that dogs and rats which are allowed to be active soon after operation show an observable and a recordable difference in the tensile strength of the operative wound, as compared with animals which are permitted progressive increase in exercise from day to day. The wounds of animals which move about early after operation not only show an increase in tensile strength but are less likely to rupture after the fifth day. Zava demonstrated that early rising promotes cicatrization.

2. Many experimenters have shown that disruption of wounds occurs from the fifth to the ninth day; and clinicians have cited the eighth to the fourteenth day after operation as the period in which this complication is most likely to occur. Yet the usual method of treatment has been to allow the patient to rise and move about during this particular phase of healing, when a wound closed with surgical gut is weakest.

3. Pulmonary emboli may occur between the third and the thirteenth postoperative day. This period again coincides with the usual time of ambulation and accounts for the sudden deaths

1. Zava, L.: The Advantages of Early Rising After Operations, *Policlinico (sez. prat.)* 47:865, 1940.

2. Nelson, H.: Early Ambulation Following Section of the Anterior Abdominal Wall, *Arch. Surg.* 49:1 (July) 1944.

3. Leithauser, D. J.: Confinement to Bed for Only Twenty-Four Hours After Operation, *Arch. Surg.* 47:203 (Aug.) 1943. Leithauser, D. J., and Bergo, H. L.: Early Rising and Ambulatory Activity After Operation, *ibid.* 42:1086 (June) 1941.

which occur when the patient sits up for the first time, causing the thrombus, which was formed about seven days before, to break off. Ambulation, if not allowed immediately after operation, should be delayed until the thrombus has been well organized. Potts and Smith⁴ showed that muscular contraction of the lower extremities of the dog stimulated circulation, with an increase of 250 per cent in the volume flow of blood in the inferior vena cava. Thus, with a quickened flow, little time is permitted for clotting, and any elements for clotting accumulated during the first day are swept away by the increased flow. Zava did not report any instance of pulmonary embolus in his 6,000 cases.

4. Pneumonitis, particularly hypostatic pneumonia in the aged, is a constant bugbear to the surgeon. Nanta^{4a} pointed out that the effect of gravity is an important factor to be overcome, for it tends to produce stasis, followed by edema of the tissues, which, in turn, encourages the growth of organisms. The circulation time is increased from one and five-tenths to four and five-tenths seconds by a change from the sitting to the standing position. Constant massage of the vascular system by the contracting muscles accelerates the flow of blood. Each muscle is a "heart" and acts like a substation in sending on the flow of blood. Realizing, further, that anesthesia predisposes to infection of the respiratory tract and phlebitis, one does well to avoid the additional complication of stasis.

Beecher⁵ pointed out that the volume of tidal air is greatly diminished in patients who have had a laparotomy and that rapid, shallow breathing is also a factor in diminution of the tidal air. Churchill and McNeil⁶ stated that the vital capacity is decreased 30 per cent when tight dressings are applied to the upper part of the abdomen. It is necessary to apply dressings loosely and avoid splinting of the abdominal muscles, which are greatly depended on for respiration. Moersch^{6a} noted that the lower the vital capacity becomes and the closer it approaches the volume of tidal air, the greater the operative risk. Powers⁷ stated the belief that in all surgical cases

preoperative determination of vital capacity should be made to ascertain the suitability of the patient for operation.

Lyford^{7a} found that the incidence of infection of the respiratory tract after anesthesia in cases in which there was no infection prior to operation was as follows: after anesthesia induced with ether, 5.8 per cent; after anesthesia induced with cyclopropane, 4.9 per cent, and after spinal anesthesia, 7.5 per cent. In cases in which there was a chronic infection or some type of infection of the respiratory tract thought not to be a contraindication to surgical intervention, further complicated infection of the respiratory tract occurred in 13.5 per cent of the cases after administration of ether, in 17.5 per cent after administration of cyclopropane and in 39.5 per cent after spinal induction anesthesia. Cutler⁸ wrote that in 4 per cent of cases in which operation on the lower portion of the abdomen and in 8 per cent of cases in which operation on the upper portion of the abdomen was performed pulmonary complications developed. Regardless of personal opinions of such statistics, it is evident that anesthesia predisposes to infection of the respiratory tract, particularly in the presence of stasis in the vascular system and retarded circulation. Every effort to avoid the pathophysical phenomena imposed by anesthesia and the reclining position should therefore be made.

Metabolism is greatly slowed down by inactivity. Early ambulation causes an early return to normal vital capacity. The standing position relieves subdiaphragmatic pressure and thus permits greater expansion of the lungs. Leithauser⁸ expressed the opinion that return to normal vital capacity parallels convalescence.

5. The power of suggestion, or the psychologic approach, in hastening recovery is not entirely without foundation. When a patient who has had a serious operation can sit up, eat well, and walk just like a "whole" person, surely a mental victory too has been achieved. The patient requires less nursing and attention and is on his way back to a useful existence.

Recently a girl who had had a laparotomy was up and about on the fourth postoperative day acting as a nurse for her roommate. She was completely rehabilitated and happy in her achievement. Thus, with early ambulation the morbidity rate is cut down and the patient is enabled to return to work much earlier. The usual long

4. Potts, W. J., and Smith, S.: Pulmonary Embolism. *Arch. Surg.* 42:661 (April) 1941.

4a. Pinoy, A., and Nanta, A.: Sclérose et endothéliose mycosiques. *Strasbourg-méd.* (pt. 2) 86:141, 1928.

5. Beecher, H. K.: Measured Effect of Laparotomy on Respiration. *J. Clin. Investigation* 12:639, 1933.

6. Churchill, E. D., and McNeil, D.: The Reduction in Vital Capacity Following Operation. *Surg., Gynec. & Obst.* 44:483, 1927.

6a. Moersch, H. J.: The Vital Capacities of 1,000 Surgical Patients. *Arch. Int. Med.* 37:128 (Jan.) 1926.

7. Powers, J. H.: Vital Capacity: Its Significance in Relation to Postoperative Pulmonary Complications. *Arch. Surg.* 17:304 (Aug.) 1928.

7a. Lyford, J., III: Postoperative Infection of the Respiratory Tract in Relationship to Inhalation and Spinal Anesthesia. *Arch. Surg.* 44:35 (Jan.) 1942.

8. Cutler, E. C., and Hoerr, S. O.: Postoperative Pulmonary Complications. *Proc. Internat. Postgrad. M. A. North America* (1941), 1942, p. 232.

period of rest in bed and inactivity, which is dreaded by any purposeful person, is appreciably curtailed. The cost of hospitalization and convalescence is reduced as much as \$75 to \$250, an important factor to the ordinary working man.

In preparation for this so-called radical post-operative treatment, the patient is instructed on the day prior to the operation as to what is expected of him. He is told that early ambulation is an aid in getting well and in preventing pulmonary conditions, which often complicate surgical treatment. He is told that during the first three days cooperation will not be easy; that he will wish to be left alone; that he will feel bad but that if he does cooperate, he will be well enough on the fourth day to walk and go home. This usually gives the patient enough strength to bear the discomfort. On the first postoperative day he is to sit up on the side of the bed; on the second day he is to move freely along the side of the bed or to sit in a chair; on the third day he is to sit in a chair and possibly to walk, as he usually does. Some patients complain bitterly; a few even faint, but by the second day most of the discomfort passes. It is interesting to note the determination to move about, even in persons who fail in their first attempt. They are ready the next day to try again. A patient who had a hernioplasty and was made ambulatory early after operation complained a great deal; however, a year later, when he was operated on for another ailment, he got up and walked on the first day without complaints or without being told to do so. In instructing the patient as to how much walking he should attempt, I tell him that he can move about as much as he desires until he has a sense of approaching fatigue. Some persons are able to return to work in two weeks, while others are longer. The patient who does not wish to become ambulatory early is allowed to remain in bed as long as he desires. However, if he shares a room with another patient who moves about and goes home soon after operation, he, too, usually decides to try ambulation. No patient has stated that he has regretted early ambulation.

The two most frequently mentioned contraindications are pulmonary emboli and the danger resulting from closure of the wound with absorbable material. The incidence of pulmonary emboli in cases of early ambulation is certainly not greater, and is demonstrated by many to be far less, than in cases in which the patient is kept quiet. To date there have been reported but 5 cases of pulmonary embolism among the 20,000 cases in which the patient became ambulatory early, or 0.025 per cent. Since in many of the 20,000 cases surgical gut was used for closure

with no reported ill effects, there seems little to be feared on that score.

Early ambulation made possible a saving of at least \$1,464 in hospital expenses for the patients in the present series. If the compound earnings yielded by an early return to work are added to this figure, the sum total should be startling. A shortened period of hospitalization also permitted a quick turnover of patients.

TABLE 1.—Age Distribution

Years	Early Ambulation		Rest in Bed	
	Females	Males	Females	Males
0-15.....	6	6	3	2
16-20.....	74	9	95	5
21-45.....	32	9	25	1
46-60.....	12	3	10	1
61-75.....	1	1	5	0
Total.....	125	28	142	9

The present comparative study was carried out on 150 patients who were treated after operation with relatively long periods of rest in bed and 153 patients who were treated by early ambulation. The age distributions in the two groups and the number in each age decade were similar (table 1).

The patients were further divided into three groups, as follows: (1) patients having appendec-

TABLE 2.—Data on Patients After Appendectomy (Average Values)

	Early Ambulation		Rest in Bed	
	Females	Males	Females	Males
Number of days in hospital.....	4.5	2.1	7.2	5.1
Age.....	19.2	17.5	23.8	15.5
Increase in temperature (degrees F.).....	1.2	1.2	1.5	1.0
Number of days fever persisted.....	2.0	1.1	2.3	1.2
Number of complications.....	0.0	1.0	2.0	0.0
Postoperative day diet was ordered.....	2.0	2.0	2.0	1.0
Number of hypodermic injections of a narcotic.....	2.2	2.5	6.5	1.0
Number of catheterizations.....	0.0	0.0	2.0	1.5
Number of patients discharged with fever.....	0.0	1.0	7.0	0.0
Number of patients with chronic surgical gut sutures.....	2.0	15.0	2.0	2.0
Number of patients with cotton sutures.....	11.0	3.0	0.0	0.0

tomy alone; (2) patients having a surgical operation on the lower portion of the abdomen, with or without appendectomy or with or without vaginal repair, and (3) patients having cholecystectomy.

Table 2 demonstrates significant differences between the ambulatory and the bed patients. The female patients having appendectomy alone who were treated by rest in bed remained in the

hospital two and four-tenths days longer on the average than those who were treated by early ambulation. One ambulatory patient and 5 bed patients had a temperature over 2 degrees (F.) above normal. The duration of fever was slightly longer for the bed patients. Food was tolerated on the first or second day by patients who became ambulatory early, whereas it was not given until the third to the fifth day to those who remained in bed. The average number of injections

TABLE 3.—Data on Patients After Laparotomy
(Average Values)

	Early Ambulation		Rest in Bed	
	Females	Males	Females	Males
Number of days in hospital.....	6.9	7.5	9.9	7.3
Age.....	29.1	53.0	29.4	24.5
Increase in temperature (degrees F.).....	1.6	1.2	3.9	3.9
Number of days fever persisted.....	4.0	3.5	9.8	5.3
Number of patients with complications.....	7.3	17.1	30.0	0.0
Postoperative day diet was ordered.....	2.4	3.2	5.0	3.2
Number of hypodermic injections of a narcotic.....	6.2	5.7	9.1	5.8
Number of catheterizations.....	0.5	0.0	2.9	3.6
Number of patients discharged with fever.....	9.0	0.0	11.0	2.0
Number of patients with chromic surgical gut sutures.....	34.0	1.0	103.0	5.0
Number of patients with cotton sutures.....	62.0	6.0	0.0	0.0

of morphine sulfate, dihydromorphinone hydrochloride or codeine sulfate administered to the bed patients was five to six and five-tenths, whereas the average number administered to the ambulatory patients was two and eight-tenths to three and seven-tenths. The fact that the ambulatory patients required fewer injections of a narcotic indicates that they overcame discomfort more rapidly. It also partially accounts for their spontaneous bowel movements and their infrequent need of purgation, since it is believed that rest in bed and drugs, such as morphine and dihydromorphinone, tend to produce constipation. Catheterization was not necessary for a single ambulatory patient, but was usually required once or twice by each bed patient. Seventeen per cent of the bed patients and 9 per cent of the ambulatory patients were discharged from the hospital with fever. The wounds of all bed patients were closed with chromic surgical gut, as were 62 per cent of the wounds of patients who walked early; the rest were closed with cotton.

The term "laparotomy" (table 3) included hernioplasty alone or in combination with appendectomy. After this operation the period of hospitalization was three days less for patients who became ambulatory early than for those who

remained in bed. The increase in temperature varied from 1.2 to 1.6 degrees (F.) for ambulatory patients and averaged 3.9 degrees (F.) for bed patients. The duration of elevation of temperature was from three and eight-tenths to four days for ambulatory patients and from five and three-tenths to nine and eight-tenths days for the bed patients. Twenty-four ambulatory patients had complications, as compared with 30 bed patients. Complications included any pathologic condition of the respiratory or the circulatory apparatus or of the extremities. Nine of the ambulatory patients and 13 of the bed patients were discharged from the hospital with fever. Catheterization was not necessary among the male patients who practiced early rising and was done on an average of 0.5 time among the female ambulatory patients; on the other hand, the male bed patients were catheterized 3.6 times and the female bed patients 2.9 times. The wounds of all the bed patients were closed with surgical gut; the wounds of 68 patients with early ambulation were closed with cotton.

Vomiting on the second day occurred in 4 per cent of the patients who became ambulatory early after operation, as against 32 per cent of the patients who remained in bed. Postoperative purgatives were needed by only 10 per cent of the patients who rose early, whereas purgatives were ordered for 85 per cent of the bed patients. Furthermore, the ambulatory patients were not given enemas before operation, whereas all the

TABLE 4.—Data on Patients After Cholecystectomy
(Average Values)

	Early Ambulation	Rest in Bed
Number of days in hospital.....	7.1	13.1
Age.....	46.1	49.0
Increase in temperature (degrees F.).....	2.1	3.6
Number of days fever persisted.....	3.7	6.7
Number of complications.....	2.0	2.0
Postoperative day diet was ordered.....	2.2	7.0
Number of hypodermic injections of a narcotic.....	7.0	17.0
Number of catheterizations.....	0.0	5.0
Number of patients discharged with fever.....	0.0	1.0
Number of patients with chromic surgical gut sutures.....	2.0	6.0
Number of patients with cotton sutures..	7.0	0.0
Number who died.....	1.0	1.0

bed patients, except those in emergency cases, were given enemas.

With regard to the patients who had cholecystectomy, table 4 indicates that those who were made ambulatory early required less hospitalization and fewer injections and that the elevation of temperature was less than for the patients who remained in bed.

Up to this point the purpose of this study has been to bring to light the advantages of early am-

bulation, to shatter doubt as to its danger, to demonstrate its practicability and to reveal its popularity and widespread acceptance. However, early ambulation should not be considered a cure-all for every postoperative problem. Some writers have given the impression that there can be no complications when early ambulation is practiced. This, however, is not true, as evidenced by the results in the 153 patients studied here. Postoperative complications, such as pulmonary emboli, pyelocystitis, thrombophlebitis and pneumonia, have occurred with early ambulation, despite the claims of some supporters of this method of postoperative treatment. I handled the following cases personally; in each instance early ambulation was practiced, yet unexpected complications developed, which one would conclude were highly improbable after reading the literature on early ambulation.

REPORT OF CASES

CASE 1.—When Mrs. J. was seven months pregnant, she had acute appendicitis. With the use of general anesthesia, an appendectomy was done. The patient was allowed to walk on the second day and was doing well. She was afebrile until the sixth day, when her temperature rose to 104 F. She aborted, and pulmonary emboli developed; her condition improved, but she suddenly died.

CASE 2.—Mrs. T. had an appendectomy, after which she did well until the sixth day, when her temperature rose to 102 F. Edema and pain developed in the lower right extremity; the diagnosis was superficial thrombophlebitis.

CASE 3.—Mrs. S. had a cholecystectomy and became febrile on the second day. On the fifth day her temperature was 102 F., with accompanying pain in the lower right extremity. The diagnosis was thrombophlebitis.

CASE 4.—Mr. M. had a cholecystectomy and was permitted to sit up in bed on the first day and in a chair on the second day. A cough and then lobar pneumonia developed. Herniation of the viscera occurred on the ninth day. The operative wound had been closed with cotton sutures.

CASE 5.—Mrs. D. had a panhysterectomy and was walking about, when severe pyelocystitis developed.

CASE 6.—Mrs. L. had a cesarean section and was up in a chair and feeling well, when, on the fourth day, pain and edema of the right lower extremity developed; the superficial veins were tender, red and painful to touch. Her temperature rose to 103 F. The diagnosis was thrombophlebitis.

CASE 7.—Master S., a 6 year old boy, had an appendectomy and was up and walking on the second day. His abdomen became greatly distended, and he began to vomit. The diagnosis was acute gastric dilatation.

In these few cases complications were observed which many of the supporters of early ambulation claimed have been eliminated. Early ambulation did not prevent phlebitis in a patient who had walked on the first and second postoperative days. Sitting up did not prevent pneumonia in a patient who was up in a chair one day prior to the rise in temperature and the onset of chill. followed closely by lobar pneumonia.

SUMMARY

This comparative study of 303 patients indicates several distinct advantages of early ambulation as a method of postoperative treatment. The periods of hospitalization and convalescence are shortened; thus, the patient's expense is curtailed and the hospital can accommodate an additional patient in his stead. The patient regains his health, returns to work much earlier and thus recovers his useful activity and earning power again. A mental attitude of well-being is maintained, and there is no long period of abnormal body function, with a special diet, rest in bed, catheterization and purgation.

Early ambulation does not increase the frequency of complications or endanger the person, as case reports and experience prove. However, neither does early ambulation eliminate all the complications as many advocates of this postoperative treatment have claimed.

608 Maison Blanche Building.

TOPICAL USE OF CONCENTRATED PENICILLIN IN SURFACE-ACTIVE SOLUTION

EDWIN J. GRACE, M.D.

BROOKLYN

AND

VERNON BRYSON, PH.D.

COLD SPRING HARBOR, N. Y.

At two meetings¹ held recently to discuss the end results of penicillin therapy, surgeons from two of the largest government hospitals for treatment of wounds of the extremities presented opinions serving to qualify prevailing optimism about the value of this agent. Although widespread use of penicillin has proved generally successful, both prophylactically and in the control of wound sepsis, there remain examples of indifferent success or outright failure which in our opinion may be based partly on inadequate technic.

Florey and Jennings² have described the principal causes of failure in the use of penicillin as follows: Dead tissue, slough or sequestrum is the focus of infection; an infected area is not being reached by the drug; the dose is too small or application too infrequent; bacteria are not sensitive and penicillin is no longer potent. Assuming that a potent preparation is used on penicillin-susceptible organisms, the problem becomes simply one of reaching the pathogens with a bacteriostatic level of penicillin and maintaining it for a sufficient period to be therapeutically effective. When topical application is made, present methods call for a maximum concentration of 500 units of penicillin per cubic centimeter of isotonic solution of sodium chloride.³ The statements of Florey and Jennings² make it appear that a higher concentration may be required.

From the Grace Clinic, Brooklyn, and the Biological Laboratory, Cold Spring Harbor, N. Y.

1. Carpenter, G. K.: The Morbidity of Compound Fractures and the Value of Penicillin Therapy, read before the Brooklyn Surgical Society, Nov. 2, 1944 and Jan. 4, 1945. Fett, H. C., in discussion on Carpenter. Meleney, F. L.: Antibiotic Therapy in Surgical Infections, read before the Brooklyn Surgical Society, Nov. 2, 1944 and Jan. 4, 1945.

2. Florey, H. W., and Jennings, M. A.: The Principles of Penicillin Treatment, *Brit. J. Surg.* (supp.) **32**:112 (July) 1944.

3. Keefer, C. S.; Blake, F. G.; Marshall, E. K., Jr.; Lockwood, J. S., and Wood, W. B., Jr.: Penicillin in the Treatment of Infections: A Report of Five Hundred Cases, *J. A. M. A.* **122**:1217 (Aug. 28) 1943.

It is now evident that the undesirable reactions of penicillin reported by earlier workers were attributable in the main to toxic impurities and not to the active penicillin fraction.⁴ Increased pharmacologic purity renders the maximum limit of 500 units per centimeter unduly conservative, and higher concentrations are coming into limited use.⁵ The tendency to use more concentrated and massive doses of penicillin would be accelerated if clinicians were generally aware of the recent findings of Demerec⁶ on the mode of origin of penicillin-resistant strains of *Staphylococcus aureus*. He showed that resistance to penicillin is not induced but arises spontaneously by mutation, and he demonstrated a few naturally resistant organisms in every mass inoculum of the standard susceptible strain. At a level of 0.15 Oxford unit per cubic centimeter all bacteria, including the resistant members, were killed. However, at a concentration of 0.064 Oxford unit per cubic centimeter the few resistant individuals survived, forming the progenitors of subsequent generations, all of which were now resistant by heredity. By mutation and continued selection, bacteria resistant to 250 units per cubic centimeter were obtained. What is probably the clinical counterpart of such a process of artificial selection has been reported by Florey and Florey.⁷ Natural defense mechanisms of the body may be able to cope with a small number of resistant organisms, but their selection by topical application of low doses of penicillin must be recognized as a definite hazard.

4. Lyons, C.: Penicillin Therapy of Surgical Infections in the U. S. Army, *J. A. M. A.* **123**:1097 (Dec. 18) 1943.

5. Hariord, C. G.; Martin, S. D.; Hagerman, P. O., and Wood, W. B., Jr.: Treatment of Staphylococcus, Pneumococcus, Gonococcus and Other Infections, *J. A. M. A.* **127**:253 (Feb. 3) 1945.

6. Demerec, M.: Production of *Staphylococcus* Strains Resistant to Various Concentrations of Penicillin, *Proc. Nat. Acad. Sc.* **31**:16 (Jan.) 1945.

7. Florey, M. E., and Florey, H. W.: General and Local Administration of Penicillin, *Lancet* **1**:387 (March 27) 1943.

Other reasons exist for a revaluation of dosage and concentration. Except in certain limited regions, whenever penicillin is applied locally much of it is rapidly lost through diffusion away from the site of application. Since loss is a function of time, it follows that an initial high concentration of penicillin is more likely to assure bacteriostatic activity during the not inconsiderable period required for effective inhibition. In addition, both diffusion and dilution will reduce the concentration of penicillin in tissues or cavities immediately adjacent to the main focus of infection. Since these neighboring areas may in themselves be infected, it becomes important to have a concentration level not always realizable systemically and sufficient to be bacteriostatic in the presence of diluting fluids and in areas contiguous to the application site. When penicillin is injected into the pleural cavity, the diluting influence of any existing empyema must be considerable.

This principle of therapy has been further emphasized by the work of Struble and Bellows,⁸ who make the following statement: "When penicillin can be applied topically, an enormous concentration can be achieved locally, which surpasses by far any value which can be secured even by the most massive intravenous doses." By using on dogs a dosage of penicillin one hundred times greater than that commonly given to human beings (12,800 units per kilogram of body weight in highly concentrated form—20,000 units per cubic centimeter of solution), they demonstrated that none was recovered in the bone marrow up to three hours following injection. The dogs used were full grown, and histologically bone structure would resemble that of human adults. We do not feel that the significance of this fact has been fully appreciated by clinicians dealing with compound fractures and with acute and with chronic osteomyelitis.

It is true that acute hematogenous osteomyelitis of the fulminating type with septicemia and multiple abscess formation calls for systemic treatment. On the other hand, chronic local osteomyelitis of long standing may be treated locally, provided all possible extrinsic sources of infection are ruled out. Any improvement noted in chronic osteomyelitis must be regarded as temporary until proved to be otherwise. In the meantime, Dickson's⁹ remarks on the role of "quiescent foci" in the recurrence of acute symptoms sug-

gest that local use of penicillin combined when necessary with judicious surgical measures may be of value. A decision to use penicillin locally or systemically often depends on the factor of accessibility and extent of the infection. Jeffrey¹⁰ observed that penicillin may fail, even against susceptible organisms "in necrotic soft tissue and necrotic bone and in the center of abscesses and masses of fibrinopurulent material." The local use of high concentrations of penicillin in a solution known to be an effective solvent of sputum and empyema fluid might aid in effectively neutralizing these isolated avascular regions that serve as a potential source of future infection. Therefore we have employed 4,000 units of penicillin per cubic centimeter in isotonic solution of sodium chloride with 0.1 per cent of the wetting agent sodium tetradecyl sulfate, or Tergitol (sodium 2-methyl-7-ethylundecyl-4 sulfate),¹¹ for topical application.

The place of detergents in medicine has been discussed in a recent editorial.¹² Sodium tetradecyl sulfate has previously been used in surgical procedures,¹³ and its combination with penicillin is predicated mainly on the properties of wetting activity, including dispersal power and solvent action. But since penicillin is not effective against many bacterial invaders that may be present in the usual type of mixed infection, i. e., organisms of the coliform and subtilis-mesentericus groups, the use of a nonspecific germicide, such as sodium tetradecyl sulfate, becomes desirable as a general bacteriocidal agent, quite aside from its wetting properties. This is especially true when one of the organisms present in a mixed infection is capable of producing a penicillin-inactivating enzyme, such as penicillinase. Certain other wetting agents have been found to be compatible with penicillin,¹⁴ and we have tested the penicillin-sodium tetradecyl sulfate solution in vitro, finding it fully potent. It is important to note that at a concentration of 4,000 units of penicillin per cubic centimeter many species of bacteria not ordinarily considered susceptible to penicillin might be effectively inhibited, even in the absence

10. Jeffrey, J. S.: Application of Penicillin to War Wounds, *Brit. J. Surg.* (supp.) 32:124 (July) 1944.

11. The Tergitol used in this work was supplied by Wallace & Tiernan Products, Inc., Belleville, N. J.

12. Medical Use of Detergents, editorial, *J. A. M. A.* 126:1152 (Dec. 30) 1944.

13. Brantigan, O. C., and Owens, J. C.: Sodium Tetradecyl Sulfate Used in the Treatment of Acute Progenic Empyema of the Pleural Cavity, *Bull. Sch. Med., Univ. Maryland* 26:247 (April) 1942.

14. Herrill, W. E., and Heilman, D.: Tissue Culture Studies on Cytotoxicity of Bacteriocidal Agents. Cytotoxic and Antibacterial Activity of Gramicidin and Penicillin: Comparison with Other Germicides, *Am. J. M. Sc.* 206:221 (Aug.) 1943.

8. Struble, G. C., and Bellows, J. O.: Studies on the Distribution of Penicillin in the Eye and Its Clinical Application, *J. A. M. A.* 125:10 (July 8) 1944.

9. Dickson, F. D.: The Clinical Diagnosis, Prognosis and Treatment of Acute Hematogenous Osteomyelitis, *J. A. M. A.* 127:212 (Jan. 27) 1945.

of a detergent. Except in a minority of wound pathogens, resistance to penicillin is relative, not absolute.

It is admittedly difficult to evaluate the variables involved when penicillin is applied in a more concentrated form and simultaneously in a solution with surface activity. Yet military failures in chemotherapy, such as those reported by Furlong and Clark¹⁵ in the treatment of open fractures of the femur, may to some extent be preventable. Chemotherapy is certainly not a substitute for surgical repair. But if penicillin is to be used, the conclusions made by Florey and Jennings² are highly significant. In their light a therapeutic use for topically applied, concentrated, surface-active solutions of penicillin appears to be virtually self evident. In agreement with this fundamental approach we are reporting our brief experience.

CASE 1.—A 68 year old man, who was first seen by us Feb. 24, 1944, had received a compound fracture of the middle third of the left tibia and fibula nine years previously. Thereafter he had had almost constant drainage from two sinuses over the fracture site. Results of routine laboratory studies were essentially normal; all points of focal infection had been eliminated. A culture made from material from the draining sinus was reported as yielding growth of *Staph. aureus*, extremely hemolytic and strongly pigmented. The culture was tested for susceptibility to penicillin, the technic of Demerec being used. In this case of chronic osteomyelitis, the highly toxic strain of *Staphylococcus* was not resistant to penicillin.

On August 14 he was hospitalized and received a dose of 400,000 units of penicillin, 10,000 units being injected into the sinus and 5,000 into the second sinus and the remainder given intramuscularly in doses of 10,000 units every three hours. He was discharged on August 18 and appeared improved. However, the sinus broke down again, and on October 3 he was once more hospitalized for penicillin therapy. He was given 50,000 units intramuscularly at once. This was followed by an injection of 5,000 units into one sinus, while the balance was administered intramuscularly in doses of 10,000 units every three hours. Although the leg looked better after this treatment, the discharge had recurred by the end of the month. Additional laboratory studies were carried out, and it was found that the organisms remained susceptible to penicillin. On December 17 the patient was readmitted to the hospital, and this time he received penicillin with Tergitol as follows: 100,000 units of penicillin was dissolved in 25 cc. of 0.1 per cent solution of Tergitol and 1 cc. of this solution put into the sinus tract every three hours until a total of 500,000 units had been used. A small petrolatum dam was placed around the sinus in order that any overflow of the solution would form a pool, thereby insuring constant contact with penicillin.

The sinus tract healed rapidly after this therapy was instituted and has remained well ever since. This time has now (March 8, 1945) amounted to nine weeks and six days; the patient states that previously he had not

been free from the purulent discharge for longer than a two week period.

CASE 2.—In a woman, aged 51 years, with hypertensive heart disease, auricular fibrillation developed in October 1944. On November 1 she had a cerebral embolus with temporary hemiplegia and was hospitalized immediately. This was followed on November 9 with a saddle embolus of the aorta. Intensive therapy failed to prevent gangrene of the right leg, and a right midhigh amputation was carried out with local anesthesia on November 15. Although the blood supply of the stump was not entirely adequate, it was deemed unwise to attempt more extensive surgical procedures at that time.

She had a stormy convalescence; her temperature did not reach a normal level, and the amputation stump became necrotic in appearance, showing poor vitality accentuated by the limited blood supply. A culture revealed *Bacillus coli*, *Staph. aureus*, *Staph. albus*, beta streptococci and gamma streptococci. On the ninth postoperative day the suppurative character of the wound failed to show improvement and two Dakin tubes were inserted into the stump under the open skin flaps. Every three hours 100 cc. of solution made up of 200,000 units of penicillin dissolved in 2,000 cc. of sterile isotonic solution of sodium chloride with 50 cc. of 0.2 per cent Tergitol was placed in the tubes. This was continued until 2,000 cc. of the solution had been used. The general appearance of soft tissue parts about the wound improved.

On the fourteenth postoperative day a débridement of the stump was done with the patient under general anesthesia (cyclopropane) and about 6 cm. of protruding necrotic femur was removed. After this procedure the dosage of penicillin was repeated as before, for a total dose of 400,000 units. The wound took on a healthy appearance; the patient made an uneventful recovery and was discharged from the hospital on Jan. 18, 1945.

CASE 3.—An unmarried woman, aged 18 years, was first seen on Nov. 23, 1943, complaining of intermittent drainage and induration of the left leg above the knee for a period of ten years. Her history was as follows: Ten years previously she had had measles with subsequent pleurisy and fever. At the same time severe pain in the distal portion of the left thigh developed. She was hospitalized for a period of fourteen months; sequestrectomy of the left femur was done, followed by eurette, and the extremity was immobilized in a cast. From August 1935 through August 1936 she was rehospitalized on six occasions; saucerization of the left femur was done, and numerous casts were applied. This patient has had sixteen operations and has been under good surgical supervision.

Examination here revealed tonsillar and dental sepsis. The left leg was atrophic, grade III (basis IV) with 2 inch (5 cm.) shortening. There were multiple scars on both the inner and the outer aspect of the thigh just above the knee, with dense scar tissue and pronounced contraction.

The patient cooperated by having a tonsillectomy and extraction of an abscessed tooth at once. She then reported gradual improvement until March 1944, when bursitis of the left knee developed after a fall. Additional dental studies at this time demonstrated a devitalized tooth, but, contrary to advice, she delayed having it extracted for nearly five months (July), until she noted soreness about the site of the old incisions on the left leg. After extraction of this tooth, which was reported to have been badly diseased, the soreness and swelling gradually subsided and she had no

15. Furlong, R., and Clark, J. M. P.: On the Use of Penicillin to Control Infection in Open Fractures, *Brit. J. Surg. (supp.)* 32:147 (July) 1944.

complaints until Nov. 20, 1944, when she reported fever (temperature of 100 F.), malaise and anorexia combined with swelling of the left leg on the inner aspect over the distal portion of the femur; the lower portion of the leg was painful on the outer aspect. The leg was red and warm; there was definite limitation of motion.

She was hospitalized immediately for penicillin therapy and received, over a period of eight days, 365,000 units; 50,000 units combined with 12 cc. of 0.1 per cent Tergitol was injected locally at once and forty-eight hours later a second dose, of 45,000 units in 11 cc. of 0.1 per cent Tergitol, was injected. The rest, 270,000 units, was given intramuscularly, 10,000 units every four hours. She was discharged from the hospital on November 29, and was then followed at the clinic. We continued the topical application of penicillin until Jan. 4, 1945, at which time she had received 130,000 additional units, a total of 500,000 units. The remainder of the penicillin was administered in the following manner:

Date	Dosage
Dec. 4, 1944	8 cc. of solution made by dissolving 100,000 units of penicillin in 20 cc. of 0.1 per cent Tergitol was injected into the lower, outer aspect of the scar on the left leg.
Dec. 7, 1944	10 cc. of solution of same concentration injected in like manner.
Dec. 11, 1944	5 cc. of solution of same concentration injected in like manner.
Dec. 18, 1944	A new solution, 200,000 units of penicillin dissolved in 25 cc. of 0.1 per cent Tergitol, was prepared and 2 cc. of this concentration injected.
Dec. 19, 1944	3 cc. of the same concentration was injected.
Dec. 21, 1944	3 cc. of the same concentration was injected.
Dec. 28, 1944	3 cc. of the same concentration was injected.

Date	Dosage
Jan. 2, 1945	3 cc. of the same concentration was injected.
Jan. 4, 1945	3 cc. of the same concentration was injected.

In the past either such local attacks of swelling and pain had resolved themselves by breaking down and discharging or the swelling would persist for many months. After topical injection of penicillin, the swelling subsided at once. With all focal infection apparently removed before the last episode, we feel that this latent infection in the bone may have been the last focus and that the local injection of Tergitol and penicillin might eliminate it permanently.

CONCLUSION

The available evidence suggests that topically applied penicillin containing 500 Oxford units per cubic centimeter may not be sufficiently concentrated for optimum therapeutic effect in refractory chronic infections. Present pharmacologic purity and possible risk of establishing resistant strains of bacteria by selection justify an upward revision of concentration. We found definite advantages in the use of 4,000 units per cubic centimeter in isotonic solution of sodium chloride with 0.1 per cent of the detergent sodium tetradecyl sulfate for local application to chronically infected areas of bone and soft tissue, and for the treatment of infected amputations. If experience in a larger number of cases confirms the efficacy of this simple procedure, it is possible that the magnitude of mutilating major surgical procedures for osteomyelitis may be substantially limited.

SUBTOTAL GASTRECTOMY

ERWIN R. SCHMIDT, M.D., AND DERMONT W. MELICK, M.D.

MADISON, WTS.

This paper is concerned with the immediate postoperative appearance of the remnant of the stomach following subtotal gastrectomy. Twenty-one cases are presented. For each patient a fluoroscopic examination was made by Dr. L. W. Paul, of the department of radiology, to check the mechanics of evacuation of the barium sulfate from the remnant of the stomach. The roentgenogram taken at the completion of the fluoroscopic examination in each case is reproduced here as a black and white copy of the original film. All gastrectomies were performed in an identical manner. Evaluation of the operation from the standpoint of the clinical course of the patient as well as the mechanics of stomach evacuation is thus possible. Technical detail has purposely been omitted in favor of emphasizing important points of the operation.

METHOD

Figure 1 presents diagrammatically the method of performing the operation. In A is shown the method of placing the clamps; the angle for placing the second clamp should be especially noted. B shows the inversion of the superior portion of the stomach along the lesser curvature.

Figure 2 is a diagrammatic representation of the completed operation. The antecolic loop of jejunum is actually much shorter than depicted. Measurement of this loop from the ligament of Treitz to the beginning of the anastomosis has been ascertained as between 9 and 14 inches (23 and 36 cm.). In addition, the proximal jejunal loop will be decreased in length after the anastomosis has been completed. This is due to the increased tonus as a result of stimulation. A 14 inch loop has been found to decrease $2\frac{1}{2}$ inches (6.35 cm.) in length. The proximal (afferent) loop is brought to the lesser curvature in all cases. The gastric stoma is placed on the side of the greater curvature. The emptying of the stomach into the distal (efferent) loop is facilitated by these two steps. Suturing the proximal loop along the lesser curvature will buffer the dangerous angle and prevent (to some extent) dumping into the proximal loop. The filling of the distal loop is illustrated by the black

and white reproductions. Extreme care in the closure of the duodenal stump cannot be over-emphasized. A routine method is not followed. If a good length of duodenum can be obtained, a Clute clamp is used. A small Payr clamp with a Parker-Kerr stitch serves equally well. If the duodenal stump is short, an "open" type of inversion is performed, a Connell stitch being used. There is experimental evidence to prove that the latter type of duodenal closure is fol-

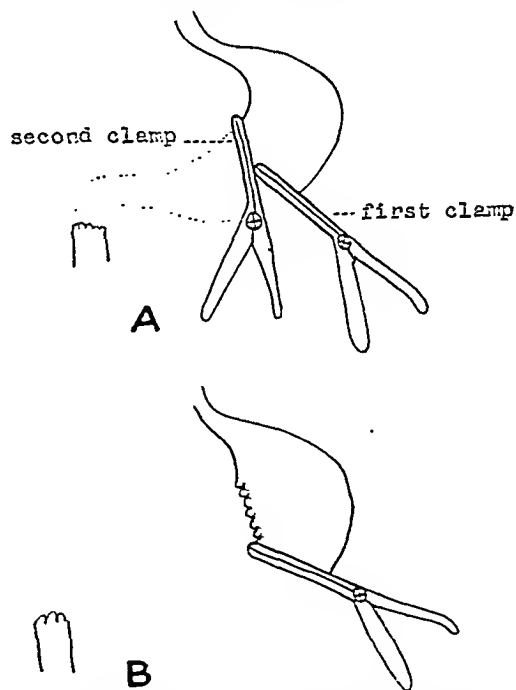


Fig. 1.—Method of performing the operation. A, position of clamps on the proximal portion of the stomach (note the angle for placing the second clamp); B, inversion of the superior portion of the stomach along the lesser curvature.

lowed by the fewest number of duodenal "blow-outs." If the safe removal of a duodenal ulcer is impossible, a Lahey gastroenterostomy¹ or a Finsterer exclusion resection (with antral excision) is performed. Removal of the ulcer

1. Lahey, F.: Simple, Useful Anterior Gastro-Enterostomy. *Surg., Gynec. & Obst.* 78:169 (Feb.) 1944.

later by a second operation, as advocated by both Lahey² and McKittrick,³ should be given serious consideration.

RESULTS

Figures 3 to 8 are black and white reproductions of the postoperative remnant of stomach and the adjacent small bowel. There are 4 cases of gastric ulcer, 5 cases of duodenal ulcer, 11 cases of carcinoma and 1 case of localized Hodgkin's disease.

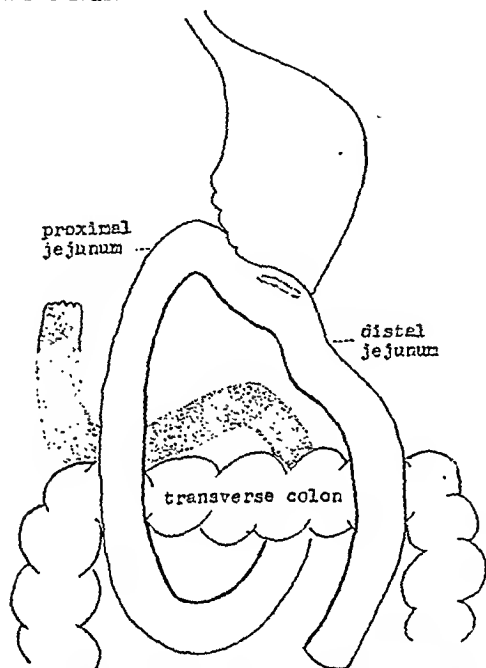


Fig. 2.—Diagrammatic representation of the completed operation.

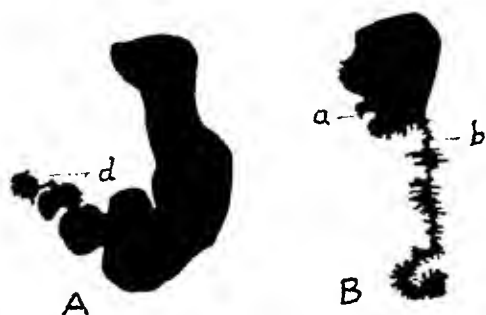


Fig. 3.—A, stomach before operation; a duodenal ulcer deformity is indicated at d. B, stomach after operation; the proximal loop of jejunum is indicated at a and the distal loop at b.

2. Lahey, F.: The Use of an Identifying "T" Tube in the Common Bile Duct in Gastric Resection for Duodenal Ulcer Adherent to the Bile Ducts, *Surg., Gynec. & Obst.* 80:197 (Feb.) 1945.

3. McKittrick, L. S.; Moore, F. D., and Warren, R.: Complication and Mortality in Subtotal Gastrectomy for Duodenal Ulcer: Report on a Two Stage Procedure, *Ann. Surg.* 120:531 (Oct.) 1944.

Figure 3 consists of photographs of the ink drawings taken directly from the original roentgenograms. They illustrate the appearance of the stomach before and after resection of the duodenal ulcer. To be noted are the amount of stomach resected and the failure of visualization of the proximal jejunal loop. The fluoroscopic examination was reported as indicating immediate emptying through the stoma, with rapid evacuation of the remnant of stomach.

In the remaining illustrations the cases of peptic ulcer have been grouped first and the cases of carcinoma second. The preoperative roentgenograms have been omitted. The postoperative

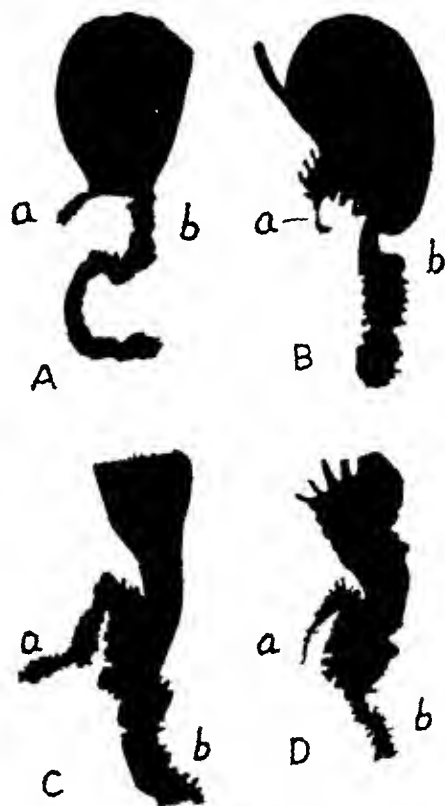


Fig. 4.—Postoperative appearance of the gastric remnant following resection for peptic ulcer (A, C, and D) for gastric ulcer and B for duodenal ulcer). The proximal jejunal loop is indicated at a and the distal loop at b.

roentgenograms are accompanied by the report of the fluoroscopic examination.

The postoperative appearance of the remnant of stomach following resection for peptic ulcer is shown in figure 4. A, C and D are from cases of gastric ulcer and B from a case of duodenal ulcer. In the cases represented in A, B and C the fluoroscopic examination revealed immediate emptying through the stoma, with rapid evacuation of the remnant of stomach; in the case

represented in *B* there was slow emptying through the stoma, but evacuation was satisfactory. This group is interesting from the standpoint of prediction of the efficacy of the anastomosis as related to the appearance of the stomach remnant. The ballooning of the remnant as shown in *B* is usually an indication that the remnant empties slowly. The failure of the remnant to fill completely (as in *C*) plus a heavy outline of the distal loop usually indicates rapid emptying of the stomach. Paradoxically, the opposite was true in these 2 cases, as will be noted from the report of the fluoroscopic examination.

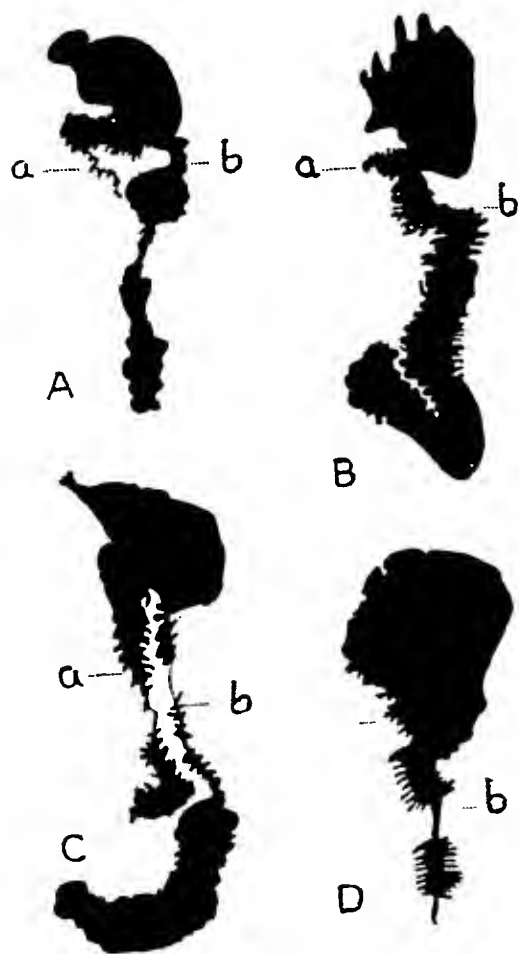


Fig. 5.—Postoperative appearance of the stomach after resection for ulcer (*A*, *C* and *D* duodenal and *B* gastric). The proximal jejunal loop is indicated at *a* and the distal at *b*; in *D* the proximal loop was not outlined.

Figure 5 *A*, *C* and *D* show the postoperative appearance of the stomach after subtotal gastrectomy for duodenal ulcer, and *B*, for gastric ulcer. In all these cases the fluoroscopic examination was reported to show immediate empty-

ing through the stoma with rapid evacuation of the stomach remnant.

Figure 6 shows results in 4 cases of carcinoma: In the first (*A*) fluoroscopic examination revealed immediate emptying through the stoma but slow evacuation of the remnant of stomach. In the second (*B*), emptying did not occur immediately,

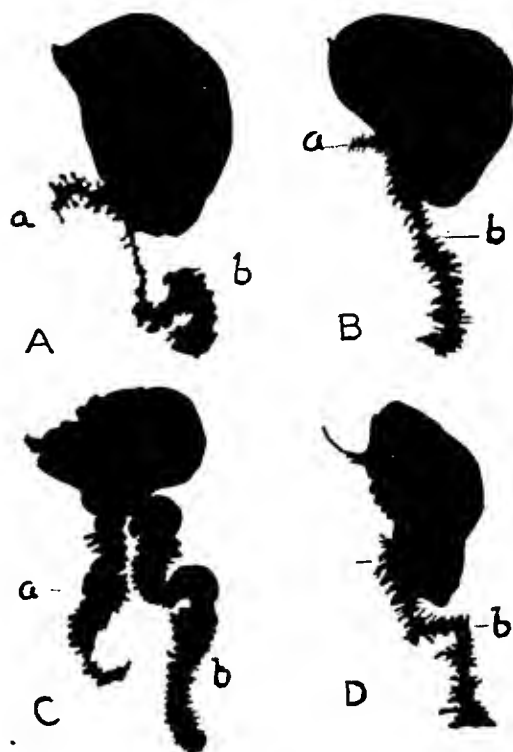


Fig. 6.—Postoperative appearance of the stomach in 4 cases of carcinoma. The proximal jejunal loop is indicated at *a* and the distal at *b*. In *D* the proximal loop was not outlined.

and there was 50 per cent retention at the end of five hours. In the third case (*C*) there was slow emptying through the stoma, with satisfactory evacuation of the stomach remnant, and in the fourth, immediate emptying through the stoma, with rapid evacuation of the stomach.

Figure 7 presents results in 3 cases of carcinoma (*A*, *C* and *D*) and 1 case of Hodgkin's disease (*B*). In all these cases immediate emptying through the stoma with rapid evacuation through the remnant of stomach was revealed.

In figure 8 are shown the results in 4 cases of carcinoma, in all of which fluoroscopic examination revealed immediate emptying through the stoma with rapid evacuation of the remnant of stomach.

In reviewing the foregoing statements it will be noted that in 4 cases fluoroscopic examination was reported to reveal slow immediate emptying of the remnant of stomach. Thus in

only 80 per cent (17 of 21) was the anastomosis considered to be "ideal." The term "ideal" denotes an anastomosis in which immediate emptying of the remnant of stomach is apparent and is followed thereafter by rapid evacuation. In only 1 of these 4 cases were both immediate emptying and eventual evacuation of the gastric remnant entirely unsatisfactory. Despite this, the patients' subjective symptoms were minimal, consisting mainly of mild epigastric distress which eventually disappeared. In the other 3 cases results were clinically satisfactory. If these 3 cases may be added to the original 17 cases of "ideal" operation then satisfactory anastomosis was accomplished in 95 per cent of the cases.

Studies of postoperative gastric acidity were unfortunately carried out in only 6 of the 9

was performed some distance from the ligament of Treitz. Additional resections, reports of which are not included in this study, have also been notable for the extreme rarity of recurrent ulceration.

The time required for performance of the operation is of more than passing interest. It

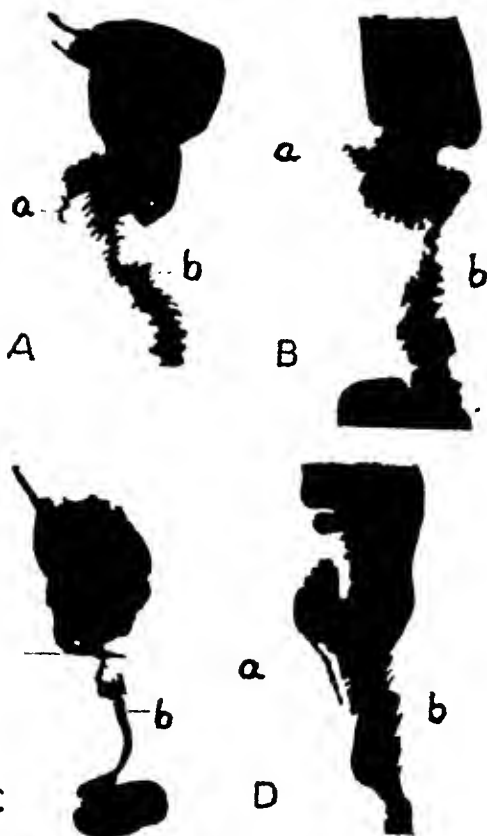


Fig. 7.—Postoperative appearance of the stomach in 3 cases of carcinoma (A, C and D) and 1 case of Hodgkin's disease (B). The proximal jejunal loop is indicated at *a* and the distal at *b*. In C the proximal loop was not outlined.

cases of peptic ulcer. Nevertheless, it is worthy of note that free hydrochloric acid was not found in any of the postoperative determinations. Furthermore, recurrent ulceration has not been a complication, despite the fact that the anastomosis

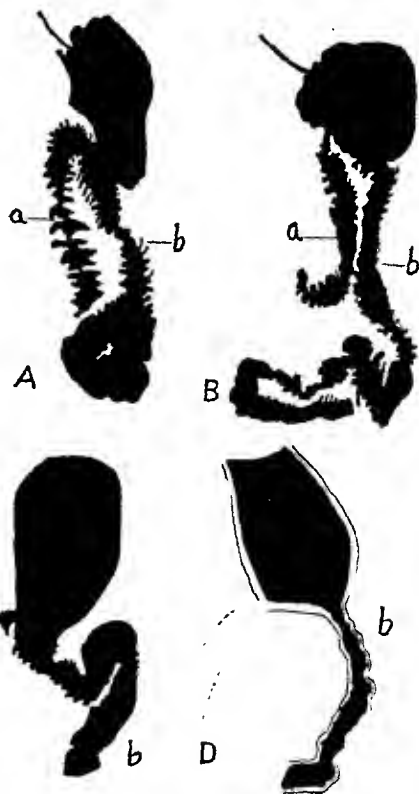


Fig. 8.—Postoperative appearance of the stomach in 4 cases of carcinoma. The proximal jejunal loop is indicated at *a* and the distal at *b*. In D the proximal loop was not outlined.

has been said that some surgeons require six hours. Hans von Haberer and De Petz⁴ found forty-five minutes to be ample time. Two and one-half hours was the average time per case in the gastrectomies herein reported.

COMMENT

In examining the postoperative black and white reproductions and evaluating them with the clinical course of the patient an interesting fact becomes apparent. Those patients exhibiting rapid evacuation of the barium from the remnant of stomach have had the most satisfactory postoperative course. This leads to the belief that an anastomosis resulting in a "dumping" stomach

4. de Petz, A.: Aseptic Technic of Stomach Resections, *Ann. Surg.* 86:388 (Sept.) 1927.

is the ideal operation to perform. This statement must be qualified to some extent. Not only must the anastomosis result in a dumping stomach, but the evacuation must be predominantly, if not totally, into the distal (efferent) loop. If the process is reversed, then the increased enteric pressure gradients resulting may secondarily prevent satisfactory evacuation of the gastric remnant.

The presentation of these cases of antecolic anastomosis should not be construed as an attempt to recommend this type of operation to the exclusion of any other type. We frequently use short loop retrocolic anastomoses with excellent results. Wangenstein⁵ favors the latter operation to the exclusion of all others. His experimental observations and clinical results⁷ give testimony as to the efficacy of the method. Nevertheless, surgeons will continue to disagree as to which method is the most satisfactory one. The failure to agree on a standardized technic indicates that each method must have its objectionable features. Individual preference will always militate against standardization of the operation. The emphasis should be placed on the performance of the best type of operation in keeping with the greatest margin of safety to the individual patient. One "routine" procedure followed by death of the patient will not be rectified by any number of subsequent perfect operations. Each case presents its own problems, and the following is an illustrative one. A subtotal gastrectomy had been planned for a patient suffering with duodenal ulcer. This was altered to a Lahey gastroenterostomy when the patient exhibited a generalized convulsion at the beginning of the operation. The postoperative course of the patient was uneventful. There was complete relief of symptoms plus a gain of 40 pounds (18 Kg.) in weight. One is justifiably skeptical that a subtotal gastrectomy would have done so well. An opinion once expressed by Dr. Donald Balfour⁶ on this point will bear repetition: "The soundest argument for so called conservative surgical treatment in peptic ulcer is that such methods when intelligently applied yield very satisfactory results and these conservative measures will probably remain an important part of the surgical treatment of the disease as long as surgery of peptic ulcer is required." Briefly, then, the decision as to method should depend on the nature of the primary disease, the amount of stomach to be removed, the surgeon's skill and

divers other factors that vary with the patient's age, diet and mental attitude.

The late results of subtotal gastrectomy should be the concern of every one. Ingelfinger⁷ has recently summarized the literature, and the following are his conclusions: Thirty per cent of patients do not regain their normal weight, and some do not regain their preoperative weight. Ten per cent suffer from symptoms soon after taking a meal, particularly if the meal is large. These symptoms consist in epigastric distress, pressure, belching, nausea and weakness. Some patients have soft stools, but few suffer from persistent diarrhea. Carbohydrates and proteins are usually adequately absorbed but some impairment in absorption of fats may occur. The dextrose tolerance test shows a rapid rise in blood sugar followed by a fall that may reach hypoglycemic levels. In a few cases symptoms occur during the hypoglycemic phase. Pernicious anemia is an extremely rare sequela, but normochromic or hypochromic anemia is not infrequent. The gastric remnant is at first small, gradually enlarges and assumes some of the reservoir function of the stomach. If the gastric remnant is extremely small, the small bowel dilates to form reservoirs near the anastomosis. Even if the stoma is anatomically perfect, gastric evacuation after subtotal gastrectomy may be delayed by functional disorders. A nourishing diet, taken frequently in small quantities fortified with vitamins and iron, often alleviates some of the complications of gastrectomy. Symptoms and various motility disorders which may be prominent during the first postoperative year subsequently tend to correct themselves spontaneously.

The only exception to these conclusions has to do with the dilatation of the remnant of stomach. We have good reason to believe that the remnant will decrease in all cases of subtotal gastrectomy if the anastomosis is functioning in an "ideal" manner. One patient in this series has now been followed over a period of thirty-one months. Series of roentgenograms of the upper part of the gastrointestinal tract have been recorded every six months. These studies reveal a gastric remnant decreased in size. The barium empties immediately through the stoma, with no evidence of any reservoir function of the remnant. Only if there is a slow emptying will dilatation result. Increased enteric pressure gradients supposedly play some part in slow emptying of the stomach. It seems logical to assume that slow emptying, whether on a basis of partial obstruction at the

5. Wangenstein, O. H.: The Criteria of a Satisfactory Operation for Ulcer and Causes of Failure After Gastric Resection for Ulcer, *Minnesota Med.* 28:66 (Jan.) 1945.

6. Balfour, D. C.: Surgical Treatment of Peptic Ulcer, *Surgery* 2:732 (Nov.) 1937.

7. Ingelfinger, F. J.: The Late Effects of Total and Subtotal Gastrectomy, *New England J. Med.* 231: 321 (Aug. 31) 1944.

outlet or increased intestinal pressure gradients, has a common root in the method of anastomosis. Dilatation could thereby be an indication of faulty anastomosis.

Occasionally a statement is made with apparent conviction that subtotal gastrectomy often ruins a patient for life. If such were actually true, little could be said for those surgeons persisting in use of such a procedure. To the infrequent person who is pessimistic regarding the outcome of the operation the following quotation⁷ may be of some comfort: "Even when the undesirable sequelae of gastrectomies are marked, they rarely interfere with the patient's ability to work, and practically never are they so dangerous or distressing as the disease for which the gastric resection was undertaken."

CONCLUSION

Twenty-one cases of subtotal gastrectomy utilizing an antecolic anastomosis were studied by means of postoperative roentgenologic examinations with barium sulfate. These studies indicate that the best anastomosis is one which effects a rapid emptying through the gastric stoma with evacuation of the stomach predominantly into the efferent loop. If this is accomplished, it is believed the stomach remnant will always decrease in size during the postoperative period.

Our results offer corroborative evidence to substantiate the established fact that the "long loop" antecolic method of anastomosis is a satisfactory one.

POSTOPERATIVE GOUTY ARTHRITIS

BERNARD J. FICARRA, M.D.

Fellow in Surgery, Lahey Clinic

AND

RALPH ADAMS, M.D.

BOSTON

Modern surgery has advanced beyond the confines of the operating theater. Surgical knowledge is progressing so rapidly that the surgeon must of necessity be mindful of the results of laboratory investigations. In recent years the role of chemistry has become more closely associated with surgery. Through chemical analysis many postoperative complications have been explained.

Innumerable authors have stressed the importance of protein to the surgical patient. The

excreted daily. This (multiplied by 6.25) means that 125 to 250 Gm. of protein is lost per day.¹ Thus it seems that endogenous protein metabolism in surgical patients is proceeding more rapidly at rest than during normal activity. One of the products of this endogenous protein metabolism is uric acid.

When uric acid is the end product of body purine metabolism, it is called endogenous uric acid. The term endogenous is used to distinguish

Salient Features in Four Instances of Postoperative Gouty Arthritis

Recorded at Kings County Hospital, Brooklyn

Case	Age	Sex	Diagnosis	Operation Performed	Post-operative Appearance of Gout	Joint Involved	Osteoarthritis Present	Blood Uric Acid, Mg. per 100 Cc.	Plasma Protein, Mg. per 100 Cc.	Residual Joint Manifestations
1	56	M	Gastric carcinoma	Subtotal gastrectomy	Fifth day	Left large toe	Slight	5	5	None
2	61	M	Rectal carcinoma	Abdomino-perineal resection	Third day	Right large toe	Moderate	5.2	4.5	Superficial desquamation of skin
3	57	M	Gastric carcinoma	Subtotal gastrectomy	Fourth day	Right large toe	Moderate	5.5	4.5	None
Recorded at Lahey Clinic (May 1937)										
4	60	M	Benign prostatic hypertrophy	Transurethral prostatic resection; bilateral vasectomy	Fourth day	Right thumb	Severe	5.4	?	Soft tissue swelling

removal of protein from the diet almost immediately produces an alteration in plasma protein. Well nourished surgical patients who are deprived of an adequate protein diet can easily approach a state of acute starvation during hospitalization.¹ In these circumstances the patient must replenish his protein deficiency through endogenous protein secured from his own body. This loss of protein tissue can be measured in the terms of nitrogen excretion. Studies have revealed that after operation as much as 20 to 40 Gm. of nitrogen may be

the uric acid formed from the purines produced in the course of the digestion of food proteins. Endogenous uric acid is derived from the breakdown of nuclear material found in muscle tissue and glandular structures.² An increase in endogenous uric acid produces an increase in blood uric acid above the normal level (3 mg. per hundred cubic centimeters of serum or whole blood). This hyperuricemia is similar to that seen in gout. These facts seem pertinent in view of our personal observation of 4 patients

From the Department of Surgery, Lahey Clinic.

1. Elman, R.: Acute Starvation Following Operation or Injury, with Special Reference to Caloric and Protein Needs, *Ann. Surg.* 120:350 (Sept.) 1944.

2. Best, C. H., and Taylor, N. B.: *Physiological Basis of Medical Practice*, Baltimore, Williams & Wilkins Company, 1943. Jones, W.: *Nucleic Acids; Their Chemical Properties and Physiological Conduct*, London, Longmans, Green & Co., 1920.

with postoperative gouty arthritis. Three of these were observed in the surgical service of Kings County Hospital, Brooklyn, from 1939 to 1944. Another postoperative patient with gouty arthritis was seen in November 1944 at the Lahey Clinic. A survey of the past records at the Lahey Clinic revealed another instance of this complication in 1937.

REPORT OF A CASE

The patient was a 67 year old white man who was seen at the Lahey Clinic on Oct. 23, 1944. He presented a two year history of epigastric pain following meals. During the previous two years he lost his appetite for all types of meat. His diet consisted mainly of milk, liquids, such as clear broth, and mashed potatoes. His pains usually were relieved by aluminum hydroxide solutions. A month before he was seen at the clinic his pains became worse and were not relieved by any medication except morphine administered by his family physician. Gastrointestinal studies on Oct. 19, 1944 demonstrated a gastric neoplasm. During the preceding month he lost 20 pounds (9.1 Kg.).

Physical examination revealed an elderly man with evidence of moderate loss of weight. His weight was 126 pounds (57.2 Kg.), his blood pressure 120 systolic and 70 diastolic and his pulse rate 88. Examination of the head and neck revealed nothing significant, except for the presence of dentures. In the chest no Virchow node was found, and the lungs were clear to percussion and auscultation. No cardiac thrills and no murmurs were heard. The abdomen was scaphoid; slight tenderness was present in the midepigastrium. The liver and spleen were not felt and no masses were palpable. Clearly marked osteoarthritic changes were evident in both the hands and the feet. Digital examination of the rectum failed to demonstrate a rectal shelf or any other unusual situation.

On October 26, the patient was operated on for an adenocarcinoma of the stomach without involvement of lymph nodes. A subtotal Hoffmeister antecolic gastric resection was performed. On his third postoperative day the patient tried to get out of bed. A slight dehiscence of the wound resulted, which did not necessitate immediate closure. In addition to this, atelectasis of the lower lobe of the right lung with pneumonitis developed. On the thirteenth postoperative day he complained of pain in the large toe of his left foot. The toe was hot and tender to palpation and presented the picture of typical gouty arthritis. Laboratory studies on that day showed a serum uric acid level of 5.9 mg. per hundred cubic centimeters; the plasma protein level was 5 Gm. per hundred cubic centimeters. Urinalysis revealed a 3+ reaction for albumin.

The patient responded to treatment and was discharged improved on Nov. 16, 1944.

COMMENT

Gout is a disease entity usually seen in elderly patients. The term "gout" has been employed to signify gouty arthritis and metabolic gout. These entities should be distinguished from each

other. Metabolic gout implies merely an increase of uric acid in body fluids (exclusive of hyperuricemia secondary to renal failure). An increased urate concentration, such as this, may exist from birth. Hyperuricemia itself produces no symptoms.³ However, when urates become deposited on the articular cartilages of joints symptoms then become manifest. When distress in a joint does occur, then gouty arthritis really exists.

Gouty arthritis as a postoperative complication is infrequently seen. Although its presence may seem to be a minor complication, its underlying significance may not be sufficiently appreciated. This arthritic manifestation should indicate a disturbed protein metabolism. It is a warning that hypoproteinemia is present, and protein depletion may result unless a positive protein balance is reestablished.

The postoperative appearance of gouty arthritis suggests that more organs are involved than appear on superficial examination. The absence of an adequate intake of food depletes the protein and glycogen reserve of the body. The liver supplies the needed glycogen, and muscle tissue gives forth the demanded protein. When the liver exhausts its necessary glycogen, hepatic physiologic processes are impaired. Since it is believed that destruction of uric acid is essentially a hepatic function, it can be appreciated that destruction of urates is limited in the presence of disturbed hepatic physiologic processes.² In this way a vicious cycle is accentuated when it is known that protein intake accelerates the excretion of uric acid and lowers its level in the blood.² In the surgical patient who is receiving no protein, the stimulus to uric acid excretion is removed and the hyperuricemia is further increased.

What is the effect of hyperuricemia on the kidneys and articulating cartilages of joints? In cases of renal failure it is known that uric acid is one of the first nitrogenous substances to rise. This fact recalls the unknown hepatorenal relationship. The exact nature of this association is not definitely known, although its existence is accepted by surgeons. It can be postulated that in the situation under discussion the hepatorenal relationship is further manifested in uric acid metabolism. The faulty destruction of uric acid by the liver may influence the excretion of uric acid by the kidneys. This retention of uric acid is thus not due to renal failure in the usual

3. Folin, O.; Berglund, H., and Derick, C.: Uric Acid Problem: Experimental Study on Animals and Man, Including Gouty Subjects, *J. Biol. Chem.* 60:36 (June) 1924.

accepted use of the term but is more closely allied to the mechanism of the hepatorenal syndrome which has been an occasional complication following surgical procedures on the biliary tract. Such faulty excretion of urates by the kidneys is another factor which further increases the hyperuricemia.

Hyperuricemia is the precipitating agent for the articular manifestations in gouty arthritis. However the pathologic changes in the joints cannot be attributed exclusively to the precipitating agent. A preexisting articular disease, osteoarthritis, must be incriminated as supplying the foundation for the deposition of the sodium salt of uric acid. Past studies have revealed that the formation of tophi cannot be attributed solely to uric acid saturation of the blood.⁴ This is believed because the uric acid concentration never reaches the limit of its solubility. Further proof is offered by the fact that in nephritis and leukemia a pronounced hyperuricemia may occur without production of tophi.⁴ Thus the importance of a local process, such as osteoarthritis, is stressed for the vicarious excretion of uric acid in the form of crystals of the sodium salt.

The crystalline deposits occur on the cartilaginous joint surfaces of the large toes and fingers. During an acute attack the joint becomes inflamed and tender. After the attack, symptoms subside promptly. If no previous deformity was present, no residual distress persists. Soft tissue swelling may remain for several days. Superficial desquamation of the skin may occur after subsidence of articular signs.

The treatment of this complication involves the increasing of the exogenous protein. A return to normal protein balance eliminates the need for specific medication.

Our survey of 5 instances of postoperative gouty arthritis substantiates the previously mentioned postulates. In every instance the patients were over 55 years of age. All had some degree of osteoarthritis. In all of them hypoproteinemia was displayed with the exception of 1 for whom protein was not determined. Varying degrees of hyperuricemia were present in every patient. No serious residual articular distress was recorded.

A definite physiologic pattern in the production of postoperative gouty arthritis cannot be stated without dispute. Nevertheless, it can be postulated that in the presence of a hypopro-

teinemia endogenous purine metabolism is accelerated. This accelerated metabolism results in a hyperuricemia, which is the precipitating agent for the deposition of urate crystals on a previously damaged cartilaginous joint surface. When glycogenolysis produces an impairment of hepatic function, the hyperuricemia is further increased by a diminution in destruction of uric acid. If a hepatorenal disturbance becomes evident, as displayed by oliguria, excretion of uric acid is further diminished, with a resultant higher concentration of blood urate. The fundamental cause for this diffuse metabolic disturbance can be attributed to a lowering of the normal blood protein level. This lowered protein level may find its cause either in an inadequate dietary protein intake or in excessive loss of body protein without replenishment. Large amounts of protein may be lost from draining wounds, extensive burns, peritonitis or empyema. A frequent source of protein loss easily overlooked is long-standing albuminuria (case 5). Therefore, protein loss without an adequate protein intake offers an excellent opportunity for the development of postoperative gouty arthritis.

SUMMARY

Five patients were observed with gouty arthritis following major surgical procedures. Four patients had cancer, 3 of them having gastric carcinoma. Every patient was a man over 55 years of age. All had some degree of osteoarthritis.

Manifestations referable to the joints usually occurred within five days after operation. The joint of the large toe was the site most frequently involved. Spontaneous remission without residual articular distress occurred.

Determinations of blood chemistry indicated a true hypoproteinemia in 4 patients; a determination was not made for 1. Hyperuricemia of variable degree was recorded in all 5 patients.

The postulated mechanism for postoperative gouty arthritis is hypoproteinemia stimulating endogenous purine metabolism, resulting in hyperuricemia. This hyperuricemia is the precipitating agent for the formation of tophi on an osteoarthritic joint.

This study accentuates the value of an adequate intake of protein for surgical patients. The correction of the hypoproteinemia results in a disappearance of articular symptoms.

CONCLUSION

The facility with which protein depletion occurs can be appreciated when one considers that a surgical patient usually is given a diet

4. Benedict, S. R.: Uric Acid in Its Relations to Metabolism, in Harvey Lectures, 1915-1916. Philadelphia, Williams & Wilkins Company, 1916, vol. 11, p. 546.

with little or no protein. This may be the fault of the surgeon, who may limit the preoperative diet, especially when surgical procedures on the gastrointestinal tract are contemplated. The patient's poor appetite may be another contributing factor.

During the postoperative period the disturbance may not be corrected. Usually only a liquid diet is permitted for several postoperative days. When the patient does not eat or when vomiting occurs, protein starvation is further increased because the usual intravenous medicaments contain only dextrose and isotonic solution of

sodium chloride. This protein deficiency is the fundamental basis for the development of postoperative gouty arthritis. Therefore, the appearance of gouty arthritis in a surgical patient should suggest a more serious metabolic disorder than superficial examination would indicate. Although serious, this complication can be easily rectified by establishment of a positive blood protein balance.

Dr. John F. Raycroft granted permission to present the clinical and laboratory data of the 3 cases observed in his surgical service at King's County Hospital, Brooklyn.

ACRYLIC RESIN AS AN IMPLANT FOR CORRECTION OF FACIAL DEFORMITIES

KENNETH W. PENHALE, D.D.S., M.D.

CHICAGO

Implants, foreign or otherwise, have their place in the reconstructive field of plastic surgery. In the past, the materials used as implants were chiefly bone or cartilage. Their use dates back to about 1861, when rib grafts were made to supply the skeletal framework of a reconstructed nose. Other materials that have been used include bovine cartilage, ear, rib and septal (autogenous) cartilage and homocartilage.

Bovine cartilage has been used in place of an autoplasmic transplant but with little success. Ear cartilage is often used and with definite success in cases of minor repair, where only a small defect exists. Homocartilage¹ as a material is fairly satisfactory but not as satisfactory as autogenous cartilage. Homocartilage can be obtained at autopsy, sterilized and stored, to be used as needed. This type has the advantage of eliminating the somewhat hazardous operation of costal resection, with its prolonged incapacity and morbidity. Regardless of the cartilage used, there is the ever present possibility that the graft may curl, although curling is less likely if transverse and longitudinal crevices are cut on the under side of the implanted costal cartilage.

In 1861 Ollier reported the transplantation of living bone for the construction of a nasal bridge.² Hardi transplanted the first and second phalanx of a finger but with poor results. Koenig advocated the use of the outer table of the frontal bone together with its overlapping skin for the building of a saddle nose. Israel transplanted a free bone graft taken from the anterior surface of the tibia.³ This graft was

successful, and it inaugurated a new era in the use of free transplants.

Comparison of bone with cartilage for free transplants shows that each has its place. For reconstruction of a saddle nose, for instance, bone is not as satisfactory as cartilage, as often absorption of the bone implant takes place. It has long been known that unless bone is placed in contact with bone or made to perform its weight-bearing function it often is absorbed in a comparatively short time. Ollier claimed that the presence of periosteum is essential for survival of bone. Others are of the opinion that periosteum does not play an essential part, although its presence may have some bearing on the rapidity of regeneration. Davis⁴ has expressed the opinion that a transplant of bone becomes absorbed even if it is in contact with living bone.

Ivory is another material that has been used.⁵ Gluck, of Paris, in 1884 was the pioneer in the employment of this material. He used it successfully as a foreign implant to bridge fractures of long bones. Jacques Joseph, of Berlin, was the first to use ivory for the correction of a saddle nose of both traumatic and syphilitic origin.⁶ The chief difficulty with ivory is the fact that it is difficult to prepare and shape prior to its insertion.

ACRYLIC RESIN

Acrylic resin, a polymerized methyl methacrylate, is a synthetic material used widely in American dentistry since 1939.⁷ It is a stable, clear material slightly heavier than water.⁷ This

Owing to lack of space, this paper has been abbreviated for publication in THE ARCHIVES by omission of a number of the illustrations. The complete article will appear in the author's reprints.

1. Straith, C. L., and Slaughter, W. B.: Grafts of Preserved Cartilage in Restorations of Facial Contour, *J. A. M. A.* **116**:2008-2013 (May 3) 1941.

2. Mowlem, R.: Bone and Cartilage Transplants: Their Use and Behavior, *Brit. J. Surg.* **29**:182-193 (Oct.) 1941.

3. Safian, J.: Corrective Rhinoplastic Surgery, New York, Paul B. Hoeber, Inc., 1935.

4. Davis, J. S.: Plastic Surgery: Its Principles and Practice, Philadelphia, P. Blakiston's Son & Co., 1919.

5. Salinger, S.: Ivory Implants for Saddle Nose: Results in Fifty Cases, *Ann. Otol., Rhin. & Laryng.* **40**:801-808 (Sept.) 1931.

6. Munson, F. T., and Heron, D. F.: Facial Reconstruction with Acrylic Resin, *Am. J. Surg.* **53**:291-295 (Aug.) 1941.

7. Skinner, E. W.: A Critical Analysis of Acrylic Resins Used for Denture Construction, *Illinois Dent. J.* **13**:433-440 (Oct.) 1944.

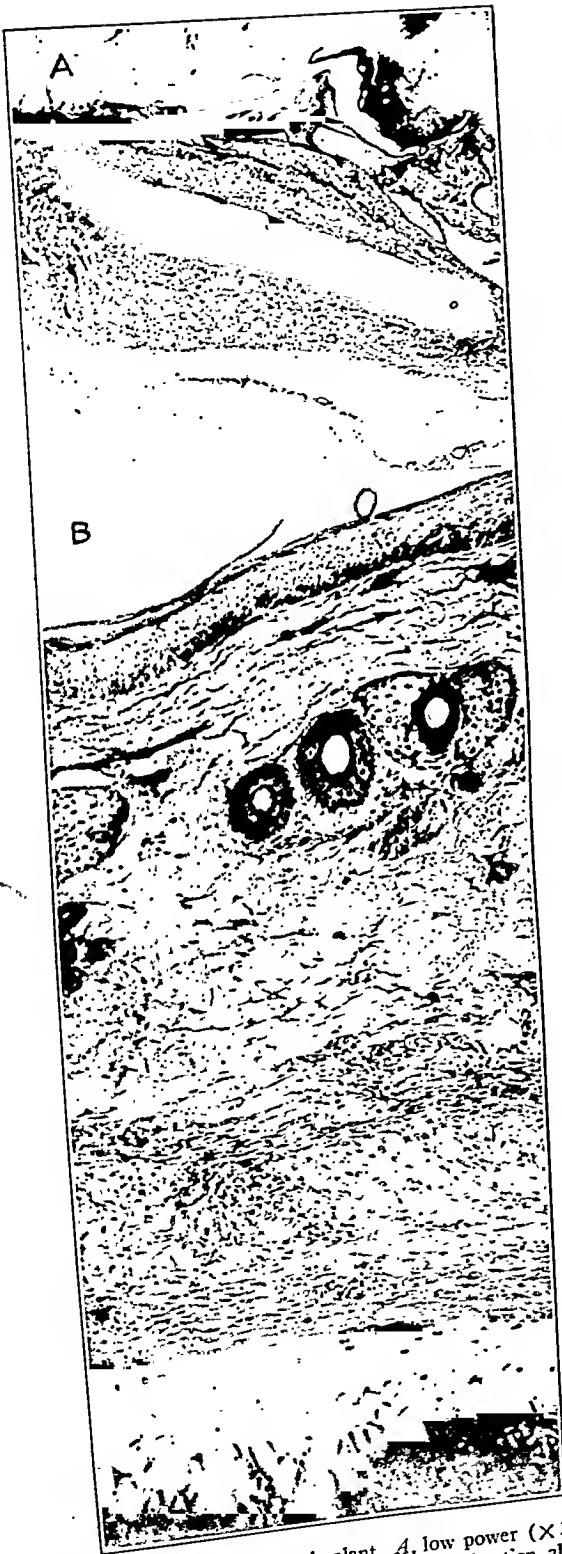


Fig. 1.—Ear cartilage implant. *A*, low power ($\times 20$), showing moderate degree of uniform infiltration about the implant; *B*, high power ($\times 135$), showing the type of infiltration.

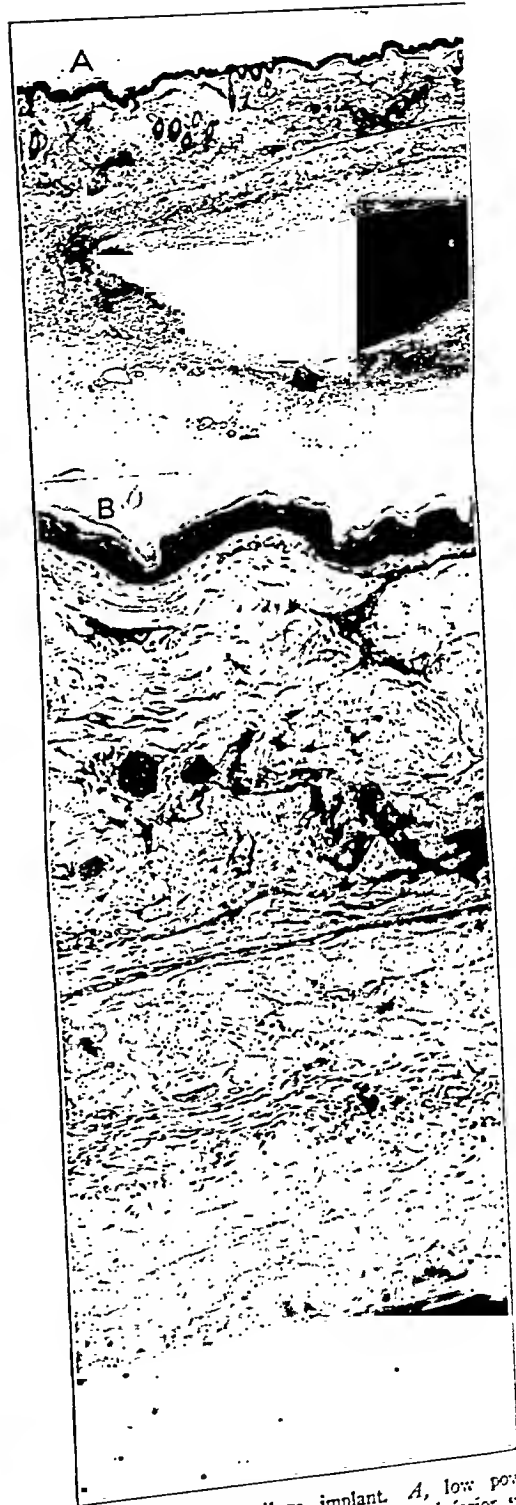


Fig. 2.—Costal cartilage implant. *A*, low power ($\times 20$), showing more infiltration on the inferior surface of the graft; *B*, high power ($\times 102$), showing type of infiltration.

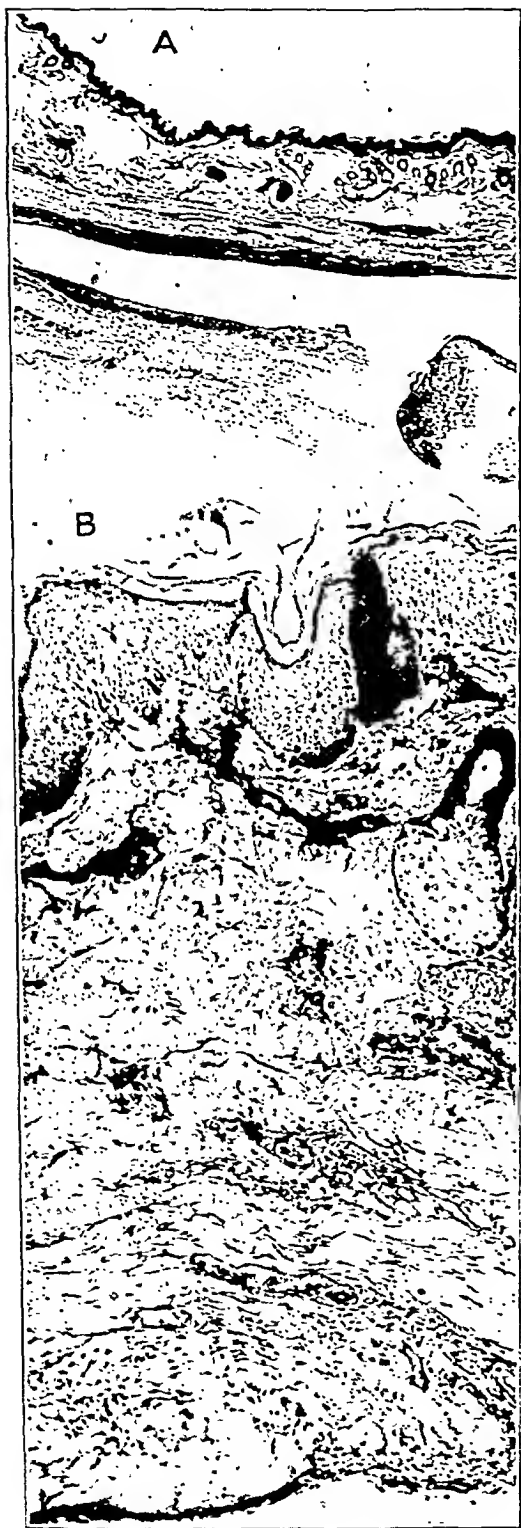


Fig. 3.—Ivory implant. *A*, low power ($\times 19$), showing more abundant infiltration about portions of the graft (ivory removed); *B*, high power ($\times 130$), showing type of infiltration.

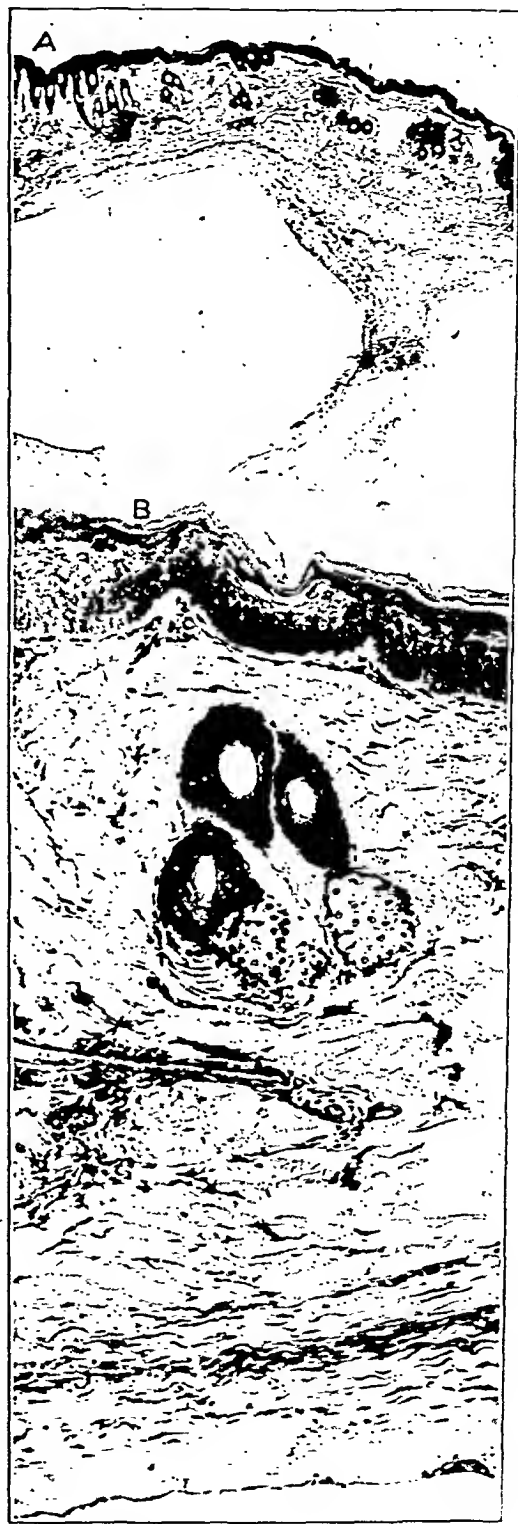


Fig. 4.—Acrylic resin implant. *A*, low power ($\times 20$), showing slight infiltration about the periphery of the implant (resin removed); *B*, high power ($\times 174$), showing area of slight infiltration (bottom).

material had its origin in Germany through the research efforts of Rohn in 1900. The chemical nature and general properties of acrylic resin are well established. Its hardness can be compared with that of 24 carat gold. It undergoes no significant change when boiled. Acrylic



Fig. 5.—Deformity of the chin of a 23 year old woman, due to bilateral ankylosis and surgically corrected in 1936. At the left, the patient is wearing an acrylic resin implant inserted at will in the labial sulcus, which was previously lined with epithelium from a thigh. At the right is the cast of the face before correction.

resin has a water solubility of about 0.1 per cent when placed in distilled water for one week.⁸ Alcohol and ether have no visible effect on the material, although acetone and chloroform produce a noticeable softening. Acrylic resin has a tensile strength of from 9,000 to 12,000 pounds (4,080 to 5,440 Kg.) per square inch (6.5 sq. cm.).⁹ It will, however, soften when submitted to a temperature of about 200 F.

FOREIGN BODY REACTION

The question arises, Does this material produce any foreign body reaction when buried in living tissues? Davis,⁹ in his report on the use of acrylic resin as a helmet for protection against craniocerebral injuries, has stated that no serious tissue reaction occurred when such pieces were buried by accident in the brain or soft tissues.

8. Peyton, F. A.: Physical and Clinical Characteristics of Synthetic Resins Used in Dentistry, *J. Am. Dent. A.* 30:1179-1189 (Aug.) 1943.

9. Davis, L.: A Helmet for Protection Against Cranio-Cerebral Injuries, *Surg., Gynec. & Obst.* 79: 89-91 (July) 1944.

Another question is, How does the reaction, any, compare with the reaction set up when known satisfactory grafts are implanted?

Experimental Studies.—To arrive at an answer, not only clinically as well as microscopically, pieces of known satisfactory grafts were implanted under the skin of monkey. These, together with a piece of acrylic resin, were implanted under careful aseptic conditions. The grafts, together with the surrounding tissue, were removed after seven days for microscopic examination.

In incision 1 ear cartilage (autogenous) was implanted; in incision 2 costal cartilage (autogenous) was implanted; in incision 3 ivory was implanted, and in incision 4 acrylic resin was implanted. The incisions in the skin were closed with silk, and a sterile dressing was applied. This dressing was covered with adhesive tape on a widely shaved area on the back of the animal where contamination and accessibility were least likely to occur.

Summarization of Histologic Sections.—From this limited series of trials one can visualize the tissue reactions caused by the various known



Fig. 7.—Congenital underdevelopment of the mandible.

satisfactory implants and compare them with those caused by the acrylic resin. One might also conclude that acrylic resin produced less inflammatory infiltration in the early stages and yet a satisfactory fibrosis. In all grafts there was little change in the true skin, and this is

especially true of the acrylic resin, around which the fibrosis is confined to the immediate area of the implant.

METHOD OF PREPARING AN ACRYLIC IMPLANT FOR CORRECTION OF FACIAL DEFECT

An impression may be taken of the face, including all parts necessary to get proper proportions. This impression may be taken with Negocoll (a colloidal material), other colloid substance or plaster of paris. The eyelashes and eyebrows are best covered with petrolatum, over which a flat piece of wet cotton is applied to prevent the material from adhering to the hair and getting into the eyes. The nasal cavity is packed lightly with a small mass of moist cotton around small tubes to facilitate breathing.

From the negative a positive is prepared, of plaster, wax, Hominit, stone or metal as desired. On this positive a wax mold of the

the lateral sides free from sharp edges. "Pink wax" (dental) is satisfactory. It can be molded by flame or softened in warm water. The wax pattern should be made slightly larger than is required, as one can easily reduce the size by means of surgical burs. Perfect molding of the wax to a cast is not necessary, and often the



Fig. 10.—Loss of the nasal bridge from traumatic injury (industrial).



Fig. 8.—Same patient as in figure 3 four months after implantation of acrylic resin through an external incision under the chin. The implant is buried under the soft tissues over the symphysis of the mandible.

defect is prepared. This is also tried to the defect itself. In the case of a saddle nose, the wax should be longer than the cast to allow compensation for the soft tissues over the globula of the nose. The under surface is concave and

mold is too small, as the implant is not to be inserted on the skin as the impression recorded. The implant is to fit over the bone, under the skin and soft tissues. A visual impression of the bony surface on which the implant is to lie is much more important. It is on this palpable hard surface that the implant must lie. Often I take no impression unless one is desired for a record. The general bony contour is noted, and the wax is prepared with the idea that it is to be inserted under the skin and subcutaneous tissues, not to be laid on the external visual defect.

The wax pattern, prepared in any manner desired, is now ready to be reproduced in acrylic resin. This is done by investing the wax in plaster of paris in a metal flask, the flask separated and the wax removed with boiling water. This leaves a mold in plaster the exact size and shape of the original wax pattern. The acrylic resin, purchased in the form of a powder and a liquid, is ready to be mixed. For this a small, clean jar can be used. The liquid, usually methyl methacrylate, is mixed with the powder to form a doughlike mass. When this consistency is

obtained, the material is packed firmly in the prepared mold slightly in excess and covered with cellophane or tinfoil. The flask is closed, clamped and placed in boiling water (100 C.) for one hour for polymerization. After boiling, it is allowed to cool and is separated. The soft, putty-like mass is now hard and can be removed in toto by cutting away the plaster.

Polishing is a not too difficult procedure. A large surgical bur can be used to remove whatever excess appears. On the under surface many cone-shaped openings are made, but these should not extend through the material. The outer surface, especially of a nasal implant over which the skin is thin, is left smooth but not glazed.

satisfactory last minute sterilization can be done by merely removing the top of the bottle and pouring in sufficient 95 proof alcohol to cover the implant.



Fig. 14.—Underdevelopment of the right side of the face (mandible and maxilla) caused by a traumatic injury when the patient was 6 years old.

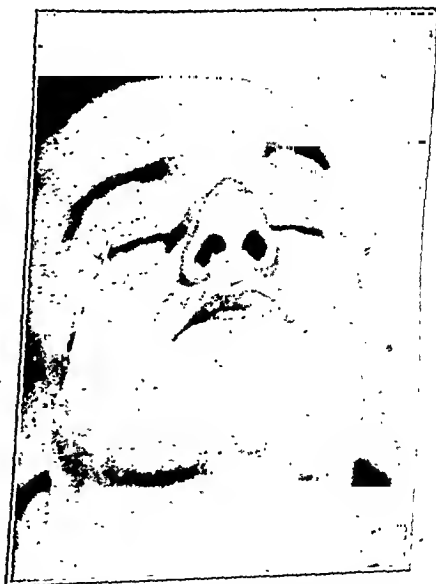


Fig. 15.—Same patient as in figure 14 after correction of the deformity of the mandible with an acrylic resin implant (overcorrected to compensate for the lack of facial development). The depression of the maxilla was corrected with an intraoral skin graft and a denture restoration of acrylic resin.

Fig. 11.—Same patient as in figure 10. Profile showing the nasal bridge after implantation of acrylic resin. The slight hump on the bridge is due to scar mass.

The acrylic resin implant is now ready to be cleaned and sterilized. Green soap and a hand brush will remove all debris; cleansing should be carefully done, especially on the under surface, where the holes are made. It is placed again into liquid soap and then immersed in boiling water for a few seconds, which is adequate sterilization. When removed from the boiling water, the implant is best kept or stored in a sterile wide-mouthed glass bottle. In the operating room the glass bottle with the acrylic resin might be autoclaved, but this is a questionable procedure and an unnecessary precaution. A

IMPLANTING THE ACRYLIC RESIN

The surgical field is prepared as one would prepare it for the reception of any implant (bone or cartilage). A precaution worthy of mention is ligation of all bleeding vessels before the implant is made. When one prepares a cavity over the symphysis of the mandible, for instance, the vessels at the mental foramen should be avoided if possible. In such a location one may not be able to stop the bleeding by a pressure bandage, as this is a hard substance and it may not conform perfectly to the bone to stop bleeding by direct pressure. The periosteum is not disturbed.

The cavity prepared, the implant is removed from the alcohol by means of a sterile tooth forceps and held in an ether bath for a few seconds. The forceps, still clasping the resin, is passed through air rather than dried with sterile gauze. After the implant has been placed in the position desired and the wound has been closed in the usual manner, a light pressure bandage should be applied. Petrolatum gauze over the skin and moist cotton will usually suffice. This may be held in position by adhesive tape or bandage. An uneven pressure bandage is objectionable, as it may dislodge the graft.

After twenty-four hours the bandage should be removed and the graft palpated to determine whether it has remained in proper position. If not, it is possible to manipulate it slightly. A gentle pressure bandage should be reapplied

and changed when necessary for a period of five to six days.

Clinical observations of the skin are surprisingly gratifying. Very little redness is seen, especially when small grafts are implanted. It is known that some persons (a very small percentage) are allergic to acrylic resins worn as a dental plate. For this reason, it is necessary to prepare the patient for such a possibility. One could test the patient for such a reaction before the operation, but in my experience no reactions have occurred after the implantation. From my observation, there is less cutaneous reaction with acrylic resin than with cartilage, especially homogeneous cartilage.

PRECAUTION

I deem it advisable to instruct patients before and after operation that such implants may produce inflammatory changes at some future date. In the event that such noticeable reactions occur, they are advised to have the grafts removed. In my limited experience with this material for over a period of about three years, no person has had any untoward clinical effects. Not until such an implant has been embedded for ten or twenty years is one prepared to state its final outcome. Further investigation is warranted, as there are unlimited possibilities for use of this material in reconstructive surgery. It may be advisable to bury metal in the acrylic resin implant, so that in case of future traumatic injuries the graft will be radiopaque to roentgen rays.

ANOMALOUS FUSION OF THE SCAPHOID AND THE GREATER MULTANGULAR BONE

LIEUTENANT COMMANDER M. G. HENRY (MC), U.S.N.R.

Congenital fusion of carpal or tarsal bones is a rare anomaly. It may occur independently but usually is associated with synostosis of some of the interphalangeal joints. There are amazingly few English and American papers on the subject.

Foreign writers offer varied arguments for their individual theories regarding the cause of this anomaly. I believe that one should accept only the scientific anatomic facts which tend to bear out the theory of arrested or defective development. These anatomic facts show that ossification centers appear in different years for each of the carpal bones except the greater multangular and the scaphoid bone, both of which show ossification centers in the sixth year of life. Because of this embryonic similarity, it seems logical that fusion of bones in the wrist would most probably involve those whose bony growth occurred at identical periods of development.

Rochlin¹ in 1928 reported symmetric fusion of some of the carpal bones associated with hypoplasia of the finger joints.

Kewesch² in 1934 expressed the opinion that the same developmental disturbance which produces synostosis of interphalangeal joints also causes fusion of carpal bones. He reported a case of symmetric synostosis of carpal and tarsal bones in 3 members of the same family.

Both Kewesch² and Esau³ in 1933 pointed out that the symmetric distribution of fusion of the carpal and tarsal bones and the frequency with which the anomaly is associated with aplasia of the interphalangeal joints tend to

indicate a congenital and hereditary character of the anomaly.

Mestern⁴ in 1934 reported bilateral fusion of carpal and tarsal bones occurring together in 2 families.

Familial tendencies were observed by Cushing in 1916. He stated that it is probable that the trait may be transmitted in its most outspoke form by a parent who appears to be but slightly affected but never through parents neither of whom show evidence of the anomaly. He studied 72 families, or 302 persons, and found the defect in 25.8 per cent. Of 150 children of parents who had evidence of fusion, 78 of them, or 52 per cent, were affected. Cushing stated the belief that the ankylosing process may be caused by an incomplete prenatal development of the joint.

The following case report concerns a patient who was examined at a military base because of an injury to his wrist. Roentgenograms showed not only fracture of the scaphoid but the interesting and rare anomalous fusion of the scaphoid with the greater multangular bone.

BRIEF REPORT OF A CASE

R. B., a man aged 25, fell on his extended hand during commando drill and felt something crack in his wrist. Examination showed the pathologic process to be limited to the wrist, which was swollen and tender. There was much pain on extension, and local severe pain on pressure over the radial aspect of the carpus. Extension of the thumb was limited and painful. Roentgenograms showed simple fracture of the inner third of the scaphoid, which was congenitally fused completely with the greater multangular bone. There was no previous history of injury to this wrist. No other anomalies were present, and none were known to exist in members of the immediate family. The anomaly was limited to the one wrist. There was no aplasia of the interphalangeal joints.

Most authors agree that the underlying cause of synostosis of carpal or tarsal bones is absence of or imperfect differentiation of the intermedial

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writer and are not to be construed as reflecting the policies of the Navy Department.

1. Rochlin, D. G.: Ueber die hereditäre symmetrische Gelenkhypoplasie, *Ztschr. f. d. ges. Anat. (Abt. 2)* **13**: 654, 1927-1928.

2. Kewesch, E. L.: Ueber hereditäre Verschmelzung der Hand- und Fusswurzelknochen, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **50**:550, 1934.

3. Esau, P.: Angeborene Synostosen im Bereich des Carpus und Tarsus, *Röntgenpraxis* **5**:235, 1933.

4. Mestern, J.: Erbliche Aplasie der Interphalangealgelenke, *Ztschr. f. orthop. Chir.* **61**:421, 1934.

5. Cushing, H.: Hereditary Ankylosis of Proximal Phalangeal Joints, *Genetics* **1**:19, 1916.

zone in the development of the ossification center. It can be accepted that fusion of such bones is a result of hypoplasia or aplasia of the individual articulations.

It has been proved that the hereditary trait for this anomaly behaves as a unit character; it

persistent limitation of motion was inherently caused by the fusion of the two bones or whether it was due to fracture of the scaphoid, which fortunately had not destroyed the nutrient artery and so healed without the usual difficulties.

SUMMARY

A case of congenital fusion of the greater multangular and the scaphoid carpal bone was discovered on roentgenographic examination of an injured wrist.

Generally fusion of the carpal bones is associated with synostosis of some of the interphalangeal joints.

Fusion of carpal or tarsal bones is hereditary, and the trait is transmitted according to the

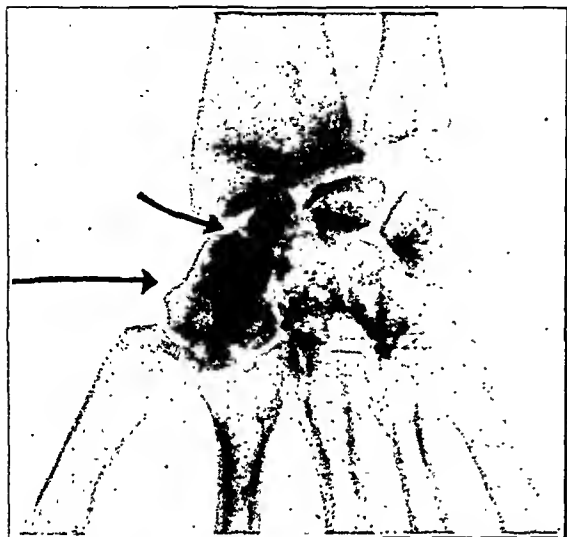


Fig. 1.—Fusion of the greater multangular and the scaphoid bone with fracture of the inner third of the scaphoid.

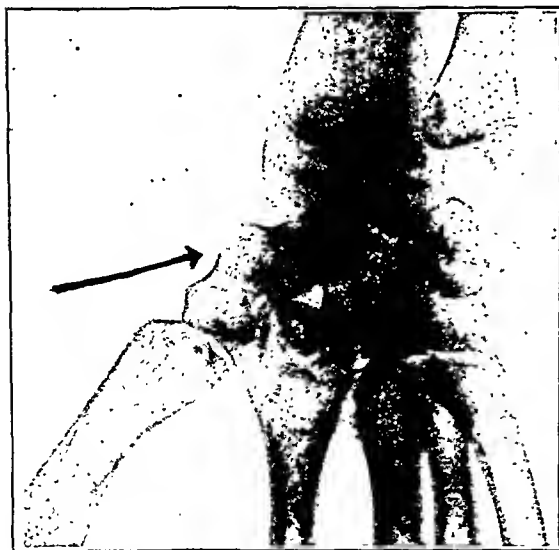


Fig. 2.—Complete fusion involving both rows of carpal bones may account for limitation in motion.

is transmitted in accordance with the mendelian law as a dominant factor and is not sex linked.

The patient had permanent limited motion in the wrist. It is impossible to state whether the

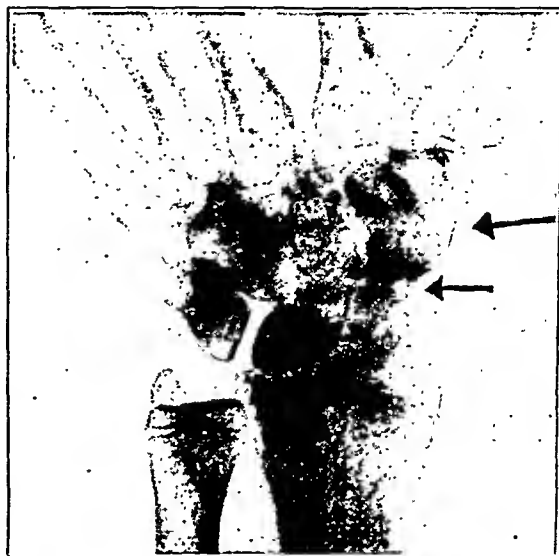


Fig. 3.—Fracture of the inner third of the scaphoid bone with no dislocation heals in normal fashion and does not produce the disabling and painful wrist which commonly results from fracture of the middle third of the scaphoid with nonunion and injury of the nutrient artery (Henry, M. G.: Fractures of the Carpal Scaphoid Bone in Industry and in the Military Service. *Arch. Surg.* 48:278 [April] 1944).

mendelian law as a dominant factor which is not sex linked.

The greater multangular bone and the scaphoid are the only two carpal bones to have identical times for the appearance of their ossification centers; this should lend argument to the theory of arrested development as the cause of this rare anomaly.

DEGENERATIVE WHITE BLOOD CELL PICTURE AS AN INDICATION OF TOXEMIA FROM BURNS

JOHN VAN DUYN II, M.D.

SYRACUSE, N. Y.

In spite of the enormous amount of work that has been done on the subject, the question of a specific toxemia in burns is not yet settled. There are at least six distinct attitudes to be found in the literature:

1. There is no true burn toxemia (Fender,¹ Lam²).

2. Infection can account for the whole picture of burn toxemia (Aldrich,³ Cruickshank,⁴ Marsh,⁵ McSwain,⁶ Wakeley,⁷ Siler⁸).

3. Hemoconcentration (secondary shock) can account for the whole picture of burn toxemia (Underhill and Kapsinow,⁹ Osterberg and others¹⁰).

4. Whatever burn toxemia really is, it cannot be explained solely on the basis of plasma loss and hemoconcentration (McClure,¹¹ Elkington,¹² Boyce,¹³ Harkins,¹⁴ Lee and Rhoads,¹⁵ Bosse and associates¹⁶).

5. Burn toxemia is a result of hepatic damage caused by anoxia, in turn a result of hemoconcentration and impaired circulation (Cope,¹⁷ Mahoney,¹⁸ Boyce¹³).

6. There is a true burn toxin absorbed from the surface of the burn and responsible for burn toxemia (Robertson and Boyd,¹⁹ Davidson, Rosenthal,²¹ Wilson,²² Blalock,²³ Tenery,²⁴ Penberthy,²⁵ Elman,²⁶ Douglas²⁷).

The period of toxemia has been generally accepted as coming after secondary shock and before the onset of infection.²⁸ Wilson²² has set the

1. Fender, F. A.: Lymphatic Pathology in Relation to the "Toxin" of Burns, *Surg., Gynec. & Obst.* 57:612-620 (Nov.) 1933.

2. Lam, C. R.: The General Care of the Burned Patient, *J. A. M. A.* 125:543-546 (June 24) 1944.

3. Aldrich, R. H.: The Role of Infection in Burns, *New England J. Med.* 208:299-309 (Feb. 9) 1933.

4. Cruickshank, R.: The Bacterial Infection of Burns, *J. Path. & Bact.* 41:367-369 (Sept.) 1935.

5. Marsh, F.: The Toxemia of Burns, *Lancet* 2: 1088-1089 (Nov. 9) 1935.

6. McSwain, G. H.: The Treatment of Burns, *J. Florida M. A.* 24:165-167 (Sept.) 1937.

7. Wakeley, C. P. G.: The Treatment of War Burns, *Surgery* 10:207-232 (Aug.) 1941.

8. Siler, V. E.: Primary Cleansing, Compression and Rest Treatment of Burns, *Surg., Gynec. & Obst.* 75:161-164 (Aug.) 1942.

9. Underhill, F. P., and Kapsinow, R.: The Alleged Toxin of Burned Skin, *J. Lab. & Clin. Med.* 16:823-830 (May) 1931.

10. Osterberg, A. E.; Bannick, E. G.; Ghormley, R. K., and Keith, N. M.: Symposium on Acute Burns, *Proc. Staff Meet., Mayo Clin.* 8:121-128 (Feb. 22) 1933.

11. McClure, R. D.: The Treatment of the Patient with Severe Burns, *J. A. M. A.* 113:1808-1812 (Nov. 11) 1939.

12. Elkington, J. R.: The Systemic Disturbance in Severe Burns and Their Treatment, *Bull. Ayer Clin. Lab. Pennsylvania Hosp.* 3:279-291 (Dec.) 1939.

13. Boyce, F. F.: The Hepatic (Hepatorenal) Factor in Burns, *Arch. Surg.* 44:799-818 (May) 1942.

14. Harkins, H. N.: The Problem of Thermal Burns, *J. A. M. A.* 125:533-536 (June 24) 1944.

15. Lee, W. E., and Rhoads, J. E.: The Present Status of the Tannic Acid Method in the Treatment of Burns, *J. A. M. A.* 125:610-612 (July 1) 1944.

16. Bosse, M. D.; Gross, P., and Hagan, M. L.: Unreliability of Blood Findings as Criteria of Burn Shock in Rabbits, *Surg., Gynec. & Obst.* 75:665-666 (Nov.) 1942.

17. Cope, O.: The Chemical Aspects of Burn Treatment, *J. A. M. A.* 125:536-543 (June 24) 1944.

18. Mahoney, E. B., and Howland, J. W.: Treatment of the Severely Burned Patient with Special Reference to Controlled Protein Therapy, *New York State J. Med.* 43:1307-1315 (July 15) 1943.

19. Robertson, B., and Boyd, G. L.: The Toxemia of Severe Superficial Burns, *J. Lab. & Clin. Med.* 9:1-14 (Oct.) 1923.

20. Davidson, E. C.: Tannic Acid in the Treatment of Burns, *Surg., Gynec. & Obst.* 41:202-221 (Aug.) 1925.

21. Rosenthal, S. R.: Neutralization of Histamine and Burn Toxin, *Ann. Surg.* 106:257-265 (Aug.) 1937.

22. Wilson, W. C.; MacGregor, A. R., and Stewart, C. P.: The Clinical Course and Pathology of Burn and Scalds Under Modern Methods of Treatment, *Brit. J. Surg.* 25:826-865 (April) 1938.

23. Blalock, A., in discussion on Heuer, G. J., and Andrus, W. DeW.: The Effect of Adrenal Corticoid Extract in Controlling Shock Following the Injection of Aqueous Extracts of Closed Intestinal Loops, *Am. Surg.* 100:734-749 (Oct.) 1934.

24. Tenery, R. M.: Extensive Cutaneous Burns, with Special Reference to Blood Chemical Changes, *Surg., Gynec. & Obst.* 72:1018-1027 (June) 1941.

25. Penberthy, G. C.; Weller, C. N., and Lewis, L. A.: Burn Therapy, *S. Clin. North America* 22:1215-1233 (Aug.) 1942.

26. Elman, R.: Early Mortality of Burns as Influenced by Rapid Tanning and by Transfusions, *Am. Surg.* 117:327-331 (March) 1943.

27. Douglas, B.: The Treatment of Burns and Other Extensive Wounds with Special Emphasis on the Trophic Jacket System, *Surgery* 15:96-143 (Jan.) 1944.

28. Harkins, H. N.: The Treatment of Burns, *Springfield, Ill. Charles C Thomas, Publisher*, 1944, pp. 38, 70, 79, 134, 202 and 213.

phases of burns more accurately as follows: (1) primary shock, up to two hours; (2) secondary shock, two to twenty-four hours; (3) acute toxemia, six to one hundred hours, and (4) septic toxemia, after one hundred hours.

Primary shock, which is neurogenic in origin, is usually considered of infrequent importance, though it may be held responsible for a small proportion of deaths (2.5 per cent).²² It is rarely observed in men of the fighting services unless other injuries are present in addition to the burns, but it is seen in marked degree in women and children and old people who have been removed from burning and bombed houses.²⁹

Secondary shock is a result of failure of circulation in the presence of hemoconcentration and falling blood pressure.³⁰ The symptoms and signs can be explained entirely on the basis of plasma loss.³¹ These are rising pulse and respiratory rates, pallor, thirst, anxious restlessness and falling blood pressure.³⁰ The temperature is subnormal.²² Secondary shock may appear within one hour of the injury, but as a rule there is a relatively safe period in the first six hours in which the patient, though severely burned, can stand a reasonably long journey.³⁰ At the end of six hours one half of the hemoconcentration likely to occur is present,²⁴ the peak being passed by the end of forty hours.³² If the concentration of the blood does not return to near normal within seventy-two hours, the patient dies.²⁸ Deaths due to secondary shock have been estimated as occurring in as high as 60 and even 80 per cent of cases of fatal burns.³³

Acute toxemia (toxic shock) is that phase of a burn characterized by drowsiness or semicomatose state, high fever, rapid pulse, rising nonprotein nitrogen level of the blood and diminished urinary output.¹⁸ The blood pressure is lowered as in secondary shock.²² There is frequently nervousness marked by restlessness, vomiting, hiccup and convulsions.²⁷ During the toxic period there are disturbances in hepatic function,³⁴ and jaundice

may be present.²⁸ Wilson believes that for 13 deaths in 65 severely burned children he eliminated all causes but "acute toxemia."²² Boyce found that of 217 fatal burns 36 were associated with uncomplicated, and 92 with complicated, toxicity.¹³

Deaths occurring after this toxic phase are due usually to either septic complications or parenchymatous organ damage or result from the presence of large granulating surfaces. The last complication may be so severe that emergency skin grafting is at times necessary, especially in children.

Secondary shock and acute toxemia are difficult to separate clinically because secondary shock, whether treated or not, carries over into the toxic phase and both may be affected by the presence of sepsis or other complications. In addition, while secondary shock is fairly constant and predictable and can be estimated by the hematocrit, toxemia is erratic and uncertain²² and has as yet no corresponding laboratory procedure to predict its development.¹³ It is with a view to offering a largely neglected aspect of the white blood cell picture as such a needed laboratory procedure that this work is presented.

HISTORICAL SUMMARY

The first mention of the white blood cells in burns was made in the eighteen sixties by Wertheim.³⁵ While studying the changes of the red cells of experimentally burned dogs, he noted the presence of "many white corpuscles."

Near the turn of the century the white cells in human burns were studied by Hock,³⁶ Bardeen,³⁷ Dohrn³⁸ and Locke.³⁹ All found a pronounced leukocytosis immediately following the burns, Locke reporting some extremely high figures. In Locke's series of 10 cases, 6 of which were fatal, there was a white cell count of 73,000 per cubic millimeter in 1 of the fatal cases thirty minutes after the burn. In the other 5 fatal cases the counts varied from 30,000 to 51,000 per cubic millimeter thirty minutes to two hours after the

29. Wakeley, C. P. G.: War Burns and Their Treatment, Practitioner 146:27-37 (Jan.) 1941.

30. McIndoe, A. H.: First-Aid Treatment of Burns, Lancet 2:377-378 (Sept. 27) 1941.

31. Beard, J. W., and Blalock, A.: Experimental Shock: VIII. The Composition of the Fluid That Escapes from the Blood Stream After Mild Trauma to an Extremity, After Trauma to the Intestines and After Burns, Arch. Surg. 22:617-625 (April) 1931.

32. Elkington, J. R.; Wolff, W. A., and Lee, W. E.: Plasma Transfusion in the Treatment of the Fluid Shift in Severe Burns, Ann. Surg. 112:150-157 (July) 1940. Tenery.²⁴

33. McIndoe.³⁰ Wakeley.²⁹

34. Wolff, W. A.; Elkington, J. R., and Rhoads, J. E.: Liver Damage and Dextrose Tolerance in Severe Burns, Ann. Surg. 112:158-160 (July) 1940.

35. Wertheim, G.: Ueber Verbrennung und Verbürhung, Med. Jahrb. 16:36-45, 1868.

36. Hock, A.: Ueber Pathogenese des Verbrennungstodes, Wien. med. Wchnschr. 48:737-741 (April 22) 1893.

37. Bardeen, C. R.: A Review of the Pathology of Superficial Burns, with a Contribution to Our Knowledge of the Pathological Changes in the Organs of Rapidly Fatal Burns, Johns Hopkins Hosp. Rep. 7:138-179, 1898.

38. Dohrn, K.: Zur pathologischen Anatomie des Frühstodes nach Hautverbrennungen, Deutsche Ztschr. f. Chir. 60:469-499, 1901.

39. Locke, E. A.: A Report of the Blood Examinations in Ten Cases of Severe Burns of the Skin, Boston M. & S. J. 147:480-484 (Oct. 30) 1902.

burn. Locke concluded that in fatal cases the count is usually 50,000 per cubic millimeter or above.

Neither Hock, Bardeen nor Locke reported counts made more than twenty-two and one-half hours after the burn. Dohrn,³⁵ however, studied the counts longer and found "a considerable increase in white blood cells up to about the sixth hour, after which a gradual decrease followed, which in the course of two days restored the number of white cells nearly to normal."

While Hock and Bardeen noted the leukocytosis as chiefly polymorphonuclear, Locke found the percentage of neutrophils to be "not so much above normal as in the inflammatory leukocytoses." He also found evidence of degeneration in nearly all specimens, in 1 case involving nearly 50 per cent of the cells. In 4 of the 6 fatal cases Locke noted "hilac-colored granules to be very abundant" in the cytoplasm. Myelocytes were present in 2 cases.

Pfeiffer,⁴⁰ in 1913, made an important contribution regarding the total white cell count. He studied the leukocytes in experimentally burned guinea pigs and found three main types of reactions: (1) in the ones with the severest burns, a primary leukopenia; (2) in those with severe fatal burns, a primary leukocytosis with secondary leukopenia, and (3) in those with light burns (one eighth to one sixth of the body surface), an intensive leukocytosis with gradual return to normal. Pfeiffer compared this leukopenia with that of anaphylactic shock and considered it due to the absorption of traces of ecrotic tissue. Although he cautioned strongly against applying his results to human beings, he advised that the relation be worked out.

Schreiner and Pucsko,⁴¹ in 1925, were the first to associate the fall in the white cell count following severe burns with the onset of the period of toxemia. They stated that they "have frequently been able to observe leukopenia at the time when toxicity was asserting itself, and have learned to appraise it as a threatening symptom." They are apparently the first authors since Locke to find degenerative changes in the differential picture and the first to call attention to the marked neutrophilic shift to the left, which they considered of more prognostic value than the morphologic changes in the cell. Scheiner and Pucsko found that the eosinophils are good indicators in estimating prognosis, that they dis-

appear in severely burned patients and reappear as the patients recover.

In 1933 McIver⁴² found the elevated white cell count to be a "constant factor" in 16 cases of human burns. Although he did not discuss the progress of the count, a review of his case reveals a definite tendency for the white cell count to fall during the period from the second to the sixth day and to return to a higher level thereafter. In 1 case, for example, the count was 24,000 per cubic millimeter on the first day, 8,600 on the fifth day, 13,480 on the sixth day and 23,600 on the seventh day (no counts being made on the second, third and fourth days). In all, the tendency for the count to fall after a burn and to return to a leukocytotic level in the even of survival is seen in 7 of the 16 cases. In 6 of the remaining cases, counts were insufficient, and in 3 the tendency was not apparent.

In 1935 Fasal⁴³ systematically studied the blood picture in severe burns and noted that sudden regression often follows the original leukocytosis. This regression occurs together with other toxic changes, such as "a left shift of the neutrophils to the myelocyte and promyelocyte stages, basophilia of the protoplasm, vacuolation and fragmentation of nuclei." Fasal observed these changes as coming on at about the fourth day after the burn and considered their presence as the "strongest possible" indication for immediate blood transfusion.

In 1937 Lambret, Driessens and Cornillot⁴⁴ studied the white cell count in experimentally burned rabbits. They found that twelve to twenty-four hours after the burn and after an initial leukocytosis there was an almost complete disappearance of white cells, particularly the neutrophils, such as to cause an actual leukopenia. They offered no explanation for the phenomenon.

In 1938 Wilson and his co-workers⁴⁵ found that "a leukocytosis in venous and capillary blood was a frequent, though not invariable, occurrence." In the case of a 3 year old boy with "moderate" scalds, the total white cell count fell from 20,000 per cubic millimeter on the first day to a low point of 6,800 per cubic millimeter

42. McIver, M. A.: A Study in Extensive Cutaneous Burns, *Ann. Surg.* 97:670-681 (May) 1933.

43. Fasal, P.: Ausgedehnte Verbrennung: Infektionsstellung zur Bluttransfusion durch toxische Veränderungen des weissen Blutbildes, *Wien. klin. Wochenschr.* 48:282 (March 1) 1935; Veränderungen im weissen Blutbild als Indikator über lebensrettende Bluttransfusionen bei Verbrennung mit infanter Prognose, *ibid.* 48:1591 (Dec. 20) 1935.

44. Lambret, D.; Driessens, J., and Cornillot, M.: Variations du taux des hématies, des leucocytes et l'hémoglobine au cours des brûlures expérimentales chez le lapin, *Compt. rend. Soc. de Biol.* 125:671-672, 1937.

40. Pfeiffer, H.: Das Problem des Verbrühungstodes. Vienna, E. Hölzel, 1913, pp. 74 and 79.

41. Schreiner, K., and Pucsko, O.: Die Veränderungen des Blutbildes nach Verbrennungen, *Med. Klin.* 21:1882-1883 (Dec. 11); 1925-1928 (Dec. 18) 1925.

the fifth. Toxemia was not, however, considered responsible.

Harkins²⁵ stated in his textbook (1942) that "the significance of leukocytosis is probably merely that it indicates trauma. Later it may indicate infection and a low grade leukocytosis may continue for some time from that cause."

From this historical review the following facts can be drawn about the blood picture in severe burns: (1) that there is a leukocytosis immediately following the burn, which in most cases is directly proportional to the degree of severity; (2) that this leukocytosis often falls between the second and sixth days and may reach an actual leukopenia, returning thereafter to its earlier level of leukocytosis in the event of survival, and (3) that the differential white blood cell picture may show a high nonfilamented cell count, degenerative changes in the cells, absence of eosinophils and presence of myelocytes—the last findings being said to indicate a serious prognosis.

The fall in leukocytes between the second and sixth days is attributed to toxemia by Schreiner and Pucsko⁴¹ and Fasal.⁴² McIver,⁴² Wilson and co-workers²² and Harkins²⁸ all have different explanations. The changes in the differential picture, although recognized as of serious import, have not been satisfactorily explained.

The experimental work on animals, except guinea pigs, bears out the applicability of the results to human beings; in guinea pigs extremely severe burns were found to produce leukopenia without preliminary leukocytosis (Pfeiffer's first type).⁴⁰ Whether this ever occurs in human beings I do not know.

REPORT OF CASES

Four previously healthy men were admitted by ambulance from the factory where they were employed to the University Hospital of the Good Shepherd on April 3, 1944. All 4 had been burned by hot oil which sprayed over them when a high pressure line burst, 3 severely and 1 less so. They were similarly treated, with petrolatum gauze dressings under moderate pressure, plasma and dextrose in saline solutions parenterally and sulfadiazine orally.

CASE 1.—R. B., aged 26 years, suffered second and third degree burns covering 85 per cent of the body surface. The hematocrit reading was 50 volumes per cent on admission and 46 volumes per cent on the next day. The patient died on April 9, six days after his admission to the hospital.

Necropsy Observations.—Anatomic: Extensive superficial burns were noted. There were acute bronchitis (probably early bronchopneumonia) and toxic changes in the heart, liver, kidneys and adrenals.

Microscopic: The lungs showed acute bronchitis with severe congestion of the mucous membrane and some

hemorrhage and acute bronchopneumonia with rather severe hemorrhage into the alveoli. There was congestion of the spleen, and the liver showed early central necrosis. In the kidneys slight capillary thickening of the glomeruli was observed. The adrenals were congested, with swelling and patchy hydropic degeneration of cortical cells.

CASE 2.—C. G., aged 36 years, suffered second and third degree burns covering 65 per cent of the body surface. The hematocrit reading was 47 volumes per cent on the day of his admission to the hospital and 58 volumes per cent on the next. This patient appeared to be holding his own till the sixth day after the burn, when gangrene developed in the right foot; later, signs of pneumonia were noted in both lungs. He died on April 18, fifteen days after admission.

Necropsy Observations.—Anatomic: There were extensive superficial burns, massive hypostatic pneumonia, multiple thrombosis of vessels, recent infarcts of the heart and spleen, gangrene of the right foot and toxic changes in liver, spleen and kidneys.

Microscopic: Examination of the heart showed arteriosclerosis, multiple small organizing areas of infarction, recent microscopic areas of myocardial degeneration and some fragmentation. The lungs showed massive bronchopneumonia and pulmonary thrombosis. There was recent infarction of the spleen, and the liver gave evidence of slight cholangitis and a few areas of focal necrosis. The kidneys showed chronic pyelonephritis of moderate degree. The adrenals disclosed a few areas of focal necrosis in the cortex, and there was an organizing thrombus in the main artery and branches of the anterior tibial artery. The mediastinal tissue revealed chronic and acute inflammation.

CASE 3.—M. K., aged 45 years, received second and third degree burns of 35 per cent of the body surface. He was discharged from the hospital improved on May 27 but was to return for additional skin grafting.

CASE 4.—C. S., aged 43 years, was admitted with first degree burns covering 35 per cent of the body surface and second and third degree burns covering 5 per cent. He recovered and was discharged on April 29, 1944.

The pertinent laboratory data in each case are given in table 1. As will be seen, the white blood cell counts were not started till the second day after admission in 3 cases and not until the third day in 1 case.

In each instance the differential counts were done by me and at least 200 cells counted from each smear. The percentage of nonfilamented cells is taken as the proportion of nonfilamented neutrophils to total neutrophils and not to total white cells. The myelocytes are included as neutrophils as well as reported in a separate column. Juvenile forms when present are not reported separately. In determining the percentage of nonfilamented cells I have used the oil immersion lens exclusively and have adhered to the criteria laid down by Cooke and Ponder⁴³;

45. Cooke, W. E., and Ponder, E.: The Polynuclear Count, London, Charles Griffin & Co., 1927; cited by Farley, D. L.; St. Clair, H., and Reisinger, J. A.: The Normal Filament and Nonfilament Polymorphonuclear Count: Its Practical Value as a Diagnostic Aid, *Am. J. M. Sc.* 180:336-356 (Sept.) 1930.

viz., that "if there is any band of nuclear tissue except a chromatin filament uniting the nuclear masses, these parts must not be considered as separate segments." This standard gives higher nonfilamented cell counts than those done with observance of less strict rules of differentiation, but the resulting figures are more accurate because of the sharper end point.

No attempt has been made to tabulate the number of cells showing cytoplasmic granules, vacuolation or other signs of toxic damage in these cases, since such a tabulation provides no special information not obtainable from the rest of the blood picture.

nized factor in leukopoiesis, that of toxic inhibition. This toxic inhibition affects both quantity and the quality of the white cells in the peripheral blood, resulting in the "degenerative white blood cell picture."

The degenerative blood picture was first described by Schilling-Torgau⁴⁶ in 1911. It showed that there were two main types of shift of the neutrophilic white cells to the left and not just one type, as Arneth⁴⁷ had described in 1904. These two types are the regenerative and the degenerative. The regenerative type is found in ordinary pyogenic infections and other inflammatory conditions. It is characterized by

TABLE 1.—White Blood Cell Pictures in First Four Cases of Burns

Date, 1944	White Blood Cells, Number	Neutro- phils, %	Myelo- cytes, %	Lympho- cytes, %	Mono- cytes, %	Eosino- phils, %	Baso- phils, %	Nonfilament Neutrophils, %
Case 1, Second and Third Degree Burns of 85 per Cent of Body								
4/5	3,500	94.5	1.0	4.0	1.5	0	0	29
4/6	3,300	90.5	1.0	7.0	2.5	0	0	28
4/8	3,550	89.5	0	9.5	2.0	0	0	26
4/9	Died							
Case 2, Second and Third Degree Burns of 65 per Cent of Body								
4/ 6	10,400	88.0	1.0	8.0	3.0	1.0	0	51
4/ 7	14,800							
4/ 8	10,800	83.5	0.5	15.5	0.5	0.5	0	92
4/10	15,900							
4/17	24,900	74.5	0	21.0	0	0	1.5	25
4/18	Died							
Case 3, Second and Third Degree Burns of 35 per Cent of Body								
4/ 5	23,000	84.0	0	10.5	5.5	0	0	51
4/ 8	18,700	83.0	0	12.0	2.5	1.5	1.0	73
4/19	16,200	68.0	0	17.0	13.0	1.0	1.0	75
4/24	17,850	77.5	0	12.5	5.0	0.5	1.5	71
5/22	17,700	69.0	0	30.5	4.5	4.5	0.5	44
5/27	Discharged, to return for skin grafting							
Case 4, First and Second Degree Burns of 35 per Cent of Body								
4/ 5	17,800	75.0	0	17.5	7.5	0	0	57
4/10	10,600	63.0	0	19.0	9.0	2.0	0	58
4/19	10,100	61.5	0	25.5	9.5	2.5	0	47
4/29	Discharged							

THE DEGENERATIVE BLOOD PICTURE

In comparing the blood studies in the 4 cases of burns (table 1) it is evident that the total blood counts when first reported are not directly proportional to the severity of the injury. This might have been the case if counts had been made on April 3, 1944, the day of the burn, but by April 5 and 6 the counts in the cases of severer burns (cases 1 and 2) were lower, not higher, than those in the cases of milder burns (cases 3 and 4).

The presence of relatively low total leukocyte counts when much higher ones are expected, as evident in cases 1 and 2, has been generally assumed to be due either to an overstimulation of the leukopoietic mechanism such as to wear out productive ability or to a lack of resistance on the part of the patient. Neither of these explanations is the true one. These blood pictures demonstrate the presence of an often unrecognized

leukocytosis, neutrophilia and, as the stimulation increases, more immature forms of neutrophils such as juvenile forms, myelocytes and, eventually, myeloblasts. The shift to the left is seldom more than moderate (40 to 60 per cent of the neutrophils), even in the presence of myelocyte and myeloblasts.

The degenerative type of shift, on the other hand, is found, according to Schilling,⁴⁸ in a number of conditions, which include typhoid, malaria, tuberculosis and many virus diseases.

46. Schilling-Torgau, V.: Kritik der Arneth'schen Lehre von der Verschiebung des leukozytären Bildes und Wertung ihren klinischen Anwendbarkeit. *Folia haemat.* 12:139-177 (July 4) 1911.

47. Arneth, J.: Die neutrophilen Leukocyten bei Infektionskrankheiten. *Deutsche med. Wochenschr.* 30:54 and 92, 1904.

48. Schilling, V.: The Blood Picture and Its Clinical Significance. St. Louis, C. V. Mosby Company, 1929, pp. 86, 140, 151, 159, 180, 190 and 245.

such as influenza, measles, typhus and kala-azar. It is characterized by low rather than high total white cell counts and a differential count which is essentially normal except for a decided neutrophilic shift to the left. This degenerative shift is characteristically much more pronounced than the regenerative, often reaching to 90 per cent and over, and without the presence of young forms. Whereas the regenerative shift is a result of stimulation to leukopoiesis, the degenerative shift is due to toxic inhibition, representing, according to Schilling, "toxic-degenerative injuries of the bone marrow" affecting the peripheral cells.⁴⁸

Recently the degenerative type of shift has been noted in several conditions not mentioned by Schilling, notably in diseases involving the gastrointestinal tract. These include paralytic ab-

TABLE 2.—*Distinguishing Characteristics of the Degenerative and Regenerative Blood Pictures, Respectively*

Degenerative (Due to Toxic Inhibition)	Regenerative (Due to Inflammatory Stimulation)
Normal total count or leukopenia	Leukocytosis (may be a terminal drop)
Normal neutrophil count or neutropenia	Neutrophilia
Absence of juvenile forms and myelocytes	Tendency for juvenile forms and myelocytes to be present
Normal or relatively increased lymphocyte count	Relative decrease of lymphocytes
Normal or increased monocyte count	Decrease or absence of monocytes
Tendency for nonfilamented neutrophil count to be decidedly increased (65 to 95%)	Slight to moderate increase of nonfilamented neutrophils (30 to 60%)
Degenerative changes (toxic granules, vacuoles, pyknosis, etc.) in most of the cells	Absence of degenerative changes (except in very severe sepsis)

dominal distention,⁴⁹ "acute peritoneal irritation,"⁵⁰ intestinal obstruction,⁵¹ and abdominal distention from whatever cause.⁵² In uncomplicated abdominal distention I found the degenerative blood picture occurring in essentially pure form; i. e., without regenerative admixtures.⁵² From these studies it has been possible to separate the regenerative and degenerative blood pictures, and in table 2 are listed the distinguishing characteristics of each.

Schilling expressed the belief that certain blood pictures represent the antagonistic action between these two shifts, resulting in a mixed degenerative-regenerative type of shift. This mixed picture is found, for example, in influenza with pneumonia and in typhoid with peritonitis.²³ In those instances in which pronounced inhibition and stimulation are both present at the same time the total white cell count is usually somewhat elevated, though not as high as if no inhibition were present; the nonfilamented cell count may be higher (even over 95 per cent) than it ever goes in either type of shift alone; there is monocytopenia, disappearance of eosinophils and a tendency for myelocytes to be present, while the neutrophils and lymphocytes are variable. This mixed degenerative-regenerative blood picture has been illustrated and compared with the pure degenerative picture in a previous article⁵² (table 5 of the article).

COMMENT ON THE FOUR REPORTED CASES OF BURNS

In the light of table 2, the blood pictures in the 4 cases of burns already reported may be more adequately interpreted. In case 1, the unexpectedly low counts and the extremely high percentages of nonfilamented cells are now seen to be degenerative characteristics which signify toxic inhibition. The neutrophilia, presence of myelocytes, monocytopenia and absence of eosinophils are all regenerative changes, indicating marrow stimulation. Thus a pronounced toxemia together with a high degree of inflammatory stimulation is shown by the blood picture. This stimulation was explained at necropsy by the finding of bronchitis and bronchopneumonia.

In case 2 the toxic inhibition is less than in case 1, as shown by the higher total count and lower percentage of nonfilamented cells on April 6. It is still considerable, however, and affects the picture throughout. The last counts (April 10 and 17) show evidence of increasing stimulation in the higher total counts and disappearance of monocytes and eosinophils, the source of the stimulation being presumably the gangrene of the foot and the pneumonia.

In cases 3 and 4 the regenerative effect is shown by the pronounced leukocytosis in each on April 5, the second day after the burn. In case 3, there is evidence of some toxicity in the increased percentage of nonfilamented cells shown in the next three counts. In case 4 there appears to be little toxicity.

49. Van Duyn, J., II: Leukocyte Exhaustion Following Surgical Procedures, *Arch. Surg.* 37:302-310 (Aug.) 1938.

50. Kaufman, R. E., and Vom Saal, F.: Leukocyte Changes in Acute Peritoneal Irritation, *J. Lab. & Clin. Med.* 26:468-476 (Dec.) 1940.

51. Harris, F. I., and Feldheym, J. S.: Leukocyte Exhaustion in Intestinal Obstruction, *Am. J. Surg.* 54:417-423 (Nov.) 1941.

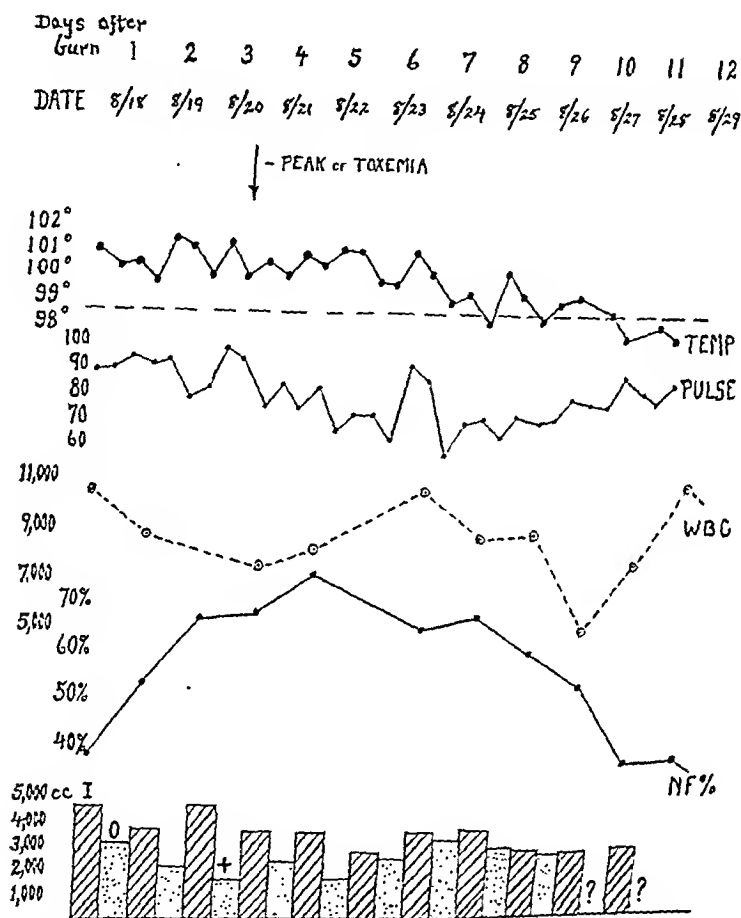
52. Van Duyn, J., II: Role of Abdominal Distention in Leukocyte Exhaustion, *Arch. Surg.* 44:339-352 (Feb.) 1942.

COMMENTS ON THREE MISCELLANEOUS CASES

Sixteen per Cent Second Degree Burns.—Although it is not so important to attempt an estimate of the degree of toxemia in burns of small extent, it may be easier to do so because of the fewer complications; and it is interesting to correlate the effect of this pure toxemia on the white blood cells with that on the rest of the clinical picture.

might be necessary. The hematocrit determined twelve hours after the patient's admission was volumes per cent.

From the chart the white cell count and percentages of nonfilamented cells show clearly onset of toxemia. It is interesting to compare these with the temperature, pulse rate and fluid intake and output. On the morning of August (three and one-half days after the burn) the to



Laboratory data for L. D. (case 5), admitted to the hospital with 16 per cent of his body covered with second degree burns. Details are given in table 3.

In the chart are the laboratory data in a case (case 5) of second degree burns of the face, neck, chest and hands covering an estimated 16 per cent of the body surface.

CASE 5.—L. D., a 21 year old man, was admitted to the Syracuse Memorial Hospital on the evening of Aug. 17, 1944 two hours after being burned in a gasoline explosion.

The treatment consisted of use of cod liver oil ointment dressings locally and sulfadiazine orally. No plasma was administered. There were no complications. No skin grafts were required. In the areas of the hands it was thought

white cell count reached its toxic low point 7,300 per cubic millimeter and the pulse began to fall. On August 22 (four and one-half days after the burn) the count of nonfilamented cells reached its peak of 75 per cent. On August 23 (five and one-half days after the burn) relative urinary output returned to normal above and the temperature began to drop. On the seventh day all values except the nonfilamented cell count had returned to normal.

Since there is probably some lag between

effect on the peripheral blood picture, it may be assumed that toxicity reached its peak in this case about seventy-two hours after the burn and had largely subsided by the morning of the seventh day. The nonfilamented cell count was valuable as an early indicator of toxemia, climbing significantly between the first and second

given the white blood cell picture and the figures for fluid intake and output in a case of a burn which was much more extensive than that of L. D. but far less toxic.

CASE 6.—N. W., a 45 year old man was admitted to Crouse-Irving Hospital on Dec. 3, 1944 and discharged as recovered on Jan. 2, 1945. He was burned when a can of kerosene exploded, the burn involving parts of the trunk and both extremities. According to the Berkow table, the second degree area covered 30 per cent of the body surface, and the first degree area 10 per cent. The hematocrit reading was 49 volumes per cent on the morning after admission. Treatment consisted of petrolatum gauze pressure dressings locally, 1,000 cc. of plasma intravenously and sulfamerazine orally. Recovery was rapid, the patient being up and about on the seventh day after the burn. There were no complications; no third degree areas appeared, and no areas required grafting.

This case illustrates the value of the white cell picture in demonstrating the mildness of a toxemia. As the table shows, toxemia was so slight that even with the help of the regenerative stimulation always present the percentage of

TABLE 3.—Details of Blood Counts in a Case of 16 per Cent Second Degree Burns (Case 5)

Date, 1944	White Blood Cells, Number	Neutrophils, %	Lymphocytes, %	Mono-cytes, %	Eosino-phils, %	Baso-phils, %	Nonfilamented Neutrophils, %
8/18	10,400	87	2	11	0	0	26
8/19	8,800	72	10	14	3	1	34
8/20	86	4	10	0	0	66
8/21	7,300	82	6	3	4	0	67
8/22	8,000	80	15	12	6	1	75
8/23							
8/24	10,300	64	23	9	4	0	63
8/25	8,500	58	30	9	2	1	65
8/26	8,600	66	19	11	4	0	58
8/27	4,600	65	24	10	1	0	51
8/28	7,400	74	14	9	1	2	35
8/29	10,500	67	20	10	3	0	36
8/30	8,900	65	21	9	5	0	52

TABLE 4.—Blood Counts and Fluid Intake and Output in a Case of 40 per Cent First and Second Degree Burns (Case 6)

Date, 1944	White Blood Cells, Number	Neutrophils, %	Lymphocytes, %	Mono-cytes, %	Eosino-phils, %	Baso-phils, %	Nonfilamented Neutrophils, %	Intake, Cc.	Output, Cc.
12/4	20,600	74	19	6	1	0	88	3,560	1,230
12/5	2,590	1,080
12/6	16,850	70	20	10	1	1	43	1,980	780
12/7	13,700	83	11	3	0	1	42	3,150	1,800
12/8	2,040	2,650
12/9	2,280	2,340
12/10	2,090	2,240
12/11	11,700	65	21	12	2	0	26	1,720	990

days. It fell to normal so slowly, however, that it was still definitely elevated as late as the tenth day after the burn. three days after all other signs of toxemia had disappeared.

The sharp drop in the white cell count on August 27 and the rise on August 29 are not mistakes. Such oscillations are frequent during the readjustment phase of a hemopoietic strain. In addition to the chart, a table (table 3) showing the more detailed differential findings is presented for case 5.

It is also interesting to compare the first count in table 3. August 18, when the stimulation of the burn trauma predominated and before the onset of toxemia, with those on August 21 and 22, when the toxic effect was at its peak. The former shows purely regenerative characteristics, except for the slight monocytosis, and the latter purely degenerative, except for the slight neutrophilia on August 21.

First and Second Degree Burns Covering 40 per Cent of the Body Surface.—In table 4 are

nonfilamented cells reached a peak of only 43 per cent (on December 6). It was insufficient to depress the total white cell count, which during the toxic phase showed a level of 13,700 per cubic millimeter. The only evidence of toxemia, besides the nonfilamented cell count, was in the lowered relative renal output of the first four days.

Intestinal Obstruction.—Patients will die after the too sudden release of an intestinal obstruction while exhibiting the same high fever, collapse, semicoma and other symptoms of toxic shock as in burns. The presence of toxemia is also similarly reflected in the blood picture,⁵³ as illustrated by the following case of uncomplicated intestinal obstruction.

CASE 7.—H. F., a 29 year old man, was admitted to the University Hospital of the Good Shepherd Aug. 26, 1944, with symptoms of low intestinal obstruction of five days' duration. Intestinal intubation failed to relieve an increasingly pronounced abdominal distention, and on September 1 the abdomen was opened. A kink at

the splenic flexure of the colon was the only pathologic condition found, and a cecostomy was performed. After the cecostomy, the distention subsided rapidly and the patient improved steadily. No explanation for the obstruction was found either at operation or on subsequent examination with a barium sulfate enema, though a history of congenital syphilis may be significant.

Table 5 gives the white cell and differential counts in the case of H. F. The blood picture on September 1, taken at the height of the distention and just before the cecostomy, shows the greatest evidence of toxicity; i. e., the largest number of degenerative characteristics. On this date the total count was at a leukopenic level (4,000 cells per cubic millimeter) and the percentage of nonfilamented cells was extremely high (96 per cent). This blood picture shows greater toxicity than the corresponding count in

stimulatory, and cause only regenerative changes. The substance responsible for the leukopoietic stimulation in these stimulatory toxins is probably identical with Menkin's "leukotaxine."⁵⁴

PROGNOSIS AND TREATMENT OF BURN TOXEMIA ACCORDING TO THE BLOOD PICTURE

If a patient with a severe burn survives the first two or three days, he is then past the dangers of primary and secondary shock and within the period of true burn toxemia. By this time there should be marked degenerative changes in the white cell picture if toxemia is to be a significant factor. According to the blood pictures in my cases, toxemia may be evident by at most the second day after the burn. It probably reaches its height somewhere between the third

TABLE 5.—Laboratory Data in a Case of Intestinal Obstruction (Case 7)

Date, 1944	White Blood Cells, Number	Neutrophils, %	Lymphocytes, %	Mono-cytes, %	Eosino-phils, %	Baso-phils, %	Nonfilamented Neutrophils, %	Comment
8/20	Admitted
8/25	15,000	First nausea
8/25	14,700	66.0	20.0	7.5	4.5	2.0	92	Hemoglobin, 107 per cent; red blood cells, 5,620,000
8/31	Marked distention
9/ 1	4,000	55.0	32.5	6.0	0	0.5	96	Nonprotein nitrogen, 38 mg. per 100 cc.; cecostomy
9/ 2	11,700	53.5	22.5	20.5	2.5	1.0	90	Hemoglobin, 90 per cent; red blood cells, 4,530,000; plasma proteins, 6.5 Gm. per 100 cc.; alkaline phosphatase, 4 B. U.
9/ 3	Cephalin flocculation 2 plus
9/ 5	14,900	66.0	22.5	8.0	3.5	0	67	
9/15	14,200	63.0	30.0	2.5	4.0	0.5	56	Barium sulfate enema
9/29	Discharged recovered

the case of uncomplicated burn (L. D.) (see table 3, August 22), but their essential similarities are obvious.

Thus, there is hematologic evidence of the presence of a similar toxic substance in intestinal obstruction and burns.

THE SEVERAL TOXINS IN BURNS

It should be remembered that there are a number of different toxic substances in burns, all affecting both the clinical and the laboratory picture. The first to appear is the toxin associated with the tissue damage of immediate injury, the "traumatic" toxin mentioned by Harkins²⁵; next, if it occurs, is the true burn toxin, and, finally, there may be bacterial, necrotic tissue and other toxins. By true burn toxin I have meant only that apparently nonspecific substance which has an inhibitory effect on the leukopoietic organs resulting in the degenerative white cell picture. The other toxins are apparently all

and sixth days,¹² but deaths occurring up to ten days afterward may still be considered due to toxemia.²³

From the first to at least the third or fourth day following a burn, the white blood cell picture must be closely watched if the onset of toxemia is to be predicted. In the cases of severest toxemia the degenerative changes come on rapidly and are extreme. An example of such a picture is apparently that in McIver's case,⁴² in which a white cell count of 1,000 per cubic millimeter (the only count reported) was present on the third day after the burn. The 2 cases mentioned by McSwain⁶ in which the patients died of "agranulocytosis" may also have been actually of this type. Such cases probably belong in the group of inevitably fatal cases and are perhaps comparable to Pfeiffer's type 1 observations.⁴¹

54. Menkin, V.: XV. Studies on Inflammation: Concerning the Mechanism of Cell Migration, *J. Exp. Med.* 67:145-158 (Jan.) 1938.

If toxemia is not extreme but still severe, the prognosis may depend on whether or not regenerative changes are present. If the changes are mixed regenerative-degenerative and of marked degree, it indicates that some complicating infection has developed, such as bronchitis or pneumonia. In such cases, the prognosis is still poor, but it is probably in just such cases that the best hope lies of further lowering the mortality rate of burns. This picture is exemplified best by the counts in cases 1 and 2 (table 1). It corresponds closely with the blood picture described by Schreiner and Pucsko⁴¹ as indicating a bad prognosis and that described by Fasal⁴² as demanding immediate and repeated blood transfusions.

In cases with severe regenerative pictures without degenerative admixtures the prognosis is probably better than in those showing evidence of severe toxemia too. It should still be guarded, however, particularly if the evidence of irritation is intense, indicating the presence of extensive necrosis or some complicating infection or both.

Unfortunately, there is still no specific antidote for the toxemia of burns any more than for that of intestinal obstruction. Transfusions of whole blood, however, do have considerable value and have apparently been somewhat neglected since hemoconcentration and the use of plasma have held the spotlight. It is possible that just as plasma was found to be required in much greater quantities for secondary shock than was originally supposed necessary, whole blood will prove effective in many cases of toxemia if given in much larger amounts than generally done at present. The blood transfusions should not be started, of course, until hemoconcentration is corrected and need not be given at all during this phase unless toxicity is predicted. The amount of blood required can be regulated by the "degeneracy" of the blood picture, just as the amounts of plasma are regulated by hematocrit determinations.

The idea of giving large blood transfusions to combat burn toxemia is not new. Harkins' text includes a list of authors who have advocated this treatment through many years, and even shows that the subject of exsanguination transfusions is not closed. Now that toxemia is predictable by means of the degenerative blood picture, blood transfusions can be started earlier, before toxemia has become irreversible, and given in more adequate amounts without fear of wasting them on nontoxic patients.

There is one other therapeutic agent besides whole blood that deserves a trial in treatment of burn toxemia, and that is liver extract. Injections of crude liver extract have already proved their value for patients showing the degenerative blood picture,⁵⁵ and also, interestingly, for experimental burns.⁵⁶ It may be that liver extract acts through its beneficial effect on hepatic function in general and its detoxifying ability in particular.⁵⁷ Doses of 10 cc. intramuscularly during each twenty-four hours of the toxic phase should be adequate to produce a maximal effect.

CONCLUSIONS

There is an inhibitory effect on the leukopoietic system frequently demonstrable in burns which is distinct from the ordinary stimulatory effect produced by traumatized, infected or necrotic tissue.

This inhibitory effect is characterized by "degenerative" changes in the white blood cells which can be differentiated from the "regenerative" changes resulting from ordinary stimulation.

Whereas the regenerative blood picture is due to inflammatory stimulation, the degenerative blood picture is a result of toxic inhibition.

There is, therefore, a true toxemia in burns, distinct from trauma and hemoconcentration, on the one hand, and sepsis, on the other, and due to the absorption of some toxic substance from the burn area.

By observing the degree of degenerative changes in the white cells the presence of toxemia can be recognized and its severity estimated. This is more difficult when the picture is a mixed degenerative-regenerative one since inhibition and stimulation are both acting together.

The degenerative white blood cell picture is found in many conditions besides burns—for

55. Powers, J. H., and Murphy, W. P.: Leukocytosis Following the Intramuscular Injection of Liver Extract, *J. Clin. Investigation* **12**:713-721 (July) 1933. Meyer, O. O.; Middleton, W. S., and Thewlis, E. M.: Leukocytosis After Parenteral Injection of Liver Extract, *Am. J. M. Sc.* **188**:49-60 (July) 1934. Powers, J. H.: Further Observations on the Leukocytic Response Induced by the Intramuscular Injection of Liver Extract, *J. Clin. Investigation* **14**:649-657 (Sept.) 1935. Van Duyn.⁴⁹

56. Prinzmetal, M.; Margoles, C., and Feigen, G.: A Principle from Liver Effective Against Shock Due to Burns, *J. A. M. A.* **122**:720-723 (Jan. 10) 1943.

57. Büttner, H. E.: Experimentelle und klinische Untersuchungen über die Wirkung einspritzbarer Leberextrakte, *Fortschr. d. Therap.* **11**:257-264 (May) 1935. Astrachan, G. D.: Crude Liver Extract as Aid to Arseno- and Heavy-Metal Therapy, *New York State J. Med.* **44**:992-1003 (May 1) 1944.

example, intestinal obstruction—showing that the inhibiting toxin is not specific.

During the toxic phase of burns the prognosis may depend on the degree of degeneracy of the white blood cell picture. If the picture is mixed degenerative-regenerative, the prognosis is worse than if a similar degree of degenerative change is present alone.

The giving of large whole blood transfusions, begun immediately after the period of hemoconcentration and repeated as indicated by the appearance and disappearance of degenerative changes in the white cells, is probably the best

general measure available to combat the toxemia of burns.

It is suggested that the injection of crude liver extract be combined with the giving of blood transfusions during the toxemic phase because of its known beneficial effect on the degenerative white blood cell picture.

Dr. Leonard M. Aquilino gave me permission to study his cases, Lieut. Robert Seidenberg called a case to my attention, and Dr. Warren R. Sisson supplied some of the data and blood smears. The staff of the library of Syracuse University College of Medicine cooperated in the study.

713 East Genesee Street.

CONGENITAL MALFORMATIONS OF THE ANUS AND RECTUM

A CLINICAL STUDY

EUGENE T. DMYTRYK, M.D.

ST. LOUIS

Congenital malformations of the anus and rectum are rather uncommon and are said to occur about once in every five thousand newly born babies. According to Allen,¹ David² and Gant,³ these deformities occur about once in every ten thousand births. A survey of the records at St. Mary's Hospital, which was opened in 1924, showed no anomalies of the anus and rectum until 1931, and from 1931 to the present time (1944) a total of 15 cases have been collected. During this period of twenty years, a total of 118,809 admissions were recorded, with 0.0013 per cent of the total admissions caused by the anomalies. Ladd and Gross,⁴ working at Children's Hospital in Boston, collected a total of 214 cases over a period of thirty-one years. Crowell and Dulin⁵ collected 28 cases over a period of twelve years at the University of Iowa Hospitals.

Anomalies of the anus and rectum are classified by Ladd and Gross⁶ into four types, as follows:

1. Incomplete rupture of the anal membrane or stenosis at a point 1 to 4 cm. above the anus.
2. Imperforate anus with the obstruction due only to a persistent membrane.
3. Imperforate anus with the rectal pouch separated from the anal membrane. The rectal pouch may end blindly either in or above the pelvis.

From the Department of Surgery, St. Louis University School of Medicine.

1. Allen, V. K.: *Malformations of the Anus and Rectum*, Tr. Am. Proct. Soc. **33**:148-153, 1932.

2. David, V. C.: *Embryology and Malformations of the Rectum*, in Nelson's Loose Leaf Living Surgery, New York, Thos. Nelson & Sons, 1937, vol. 5, pp. 161-164.

3. Gant, S. G.: *Diseases of Anus, Rectum and Colon*, Philadelphia, W. B. Saunders Company, 1923.

4. Ladd, W. E., and Gross, R. E.: *Congenital Malformations of Anus and Rectum*, Am. J. Surg. **23**: 167-183, 1934.

5. Crowell, E. A., and Dulin, J. W.: *Congenital Anomalies of the Anus and Rectum*, Surgery **7**:529-539, 1940.

6. Ladd, W. E., and Gross, R. E.: *Abdominal Surgery of Infancy and Childhood*, Philadelphia, W. B. Saunders Company, 1941; footnote 4.

4. Normal anus and anal pouch with the rectal pouch ending blindly. There may be either a membranous obstruction between or a separation of the anal and rectal pouches. When the pouches are separated, a cord of tissue without a lumen occasionally may connect them.

Of the 15 patients, 5, or 33.3 per cent, had anomalies of type 1, and 10, or 66.6 per cent, of type 3. There were no anomalies of type 2 or type 4 represented in this series. The sex distribution showed 4 males and 1 female with anomalies of type 1, and 8 males and 2 females with anomalies of type 3 (table 1).

TABLE 1.—*Distribution of the Four Types of Anomalies*

Type	Males	Females	Total
1.....	4	1	5
2.....	0	0	0
3.....	8	2	10
4.....	0	0	0
Totals.....	12	3	15

Five patients, or 33.3 per cent, had fistulas connecting the rectum with the genitourinary tract or perineum. Of these, 2 were male and 3 were female. Two (16.6 per cent) of the males and 3 (100 per cent) of the females had associated fistulas. One of these fistulas occurred in association with a type 1 anomaly and 4 in association with a type 3 anomaly. This is in agreement with the statistics reported by Ladd and Gross.⁶

TABLE 2.—*Distribution of Fistulas in Males and Females*

Type of Fistula	Males	Females	Total
Rectovesical.....	1	0	1
Rectourethral.....	1	0	1
Rectovaginal.....	0	2	2
Rectum-fossa navicularis.....	0	1	1
Totals.....	2	3	5

Two types of fistula were encountered in the males, rectovesical and rectourethral. No rectoperineal fistulas were found. Of the females, 2 had rectovaginal fistulas and 1 had a rectum-fossa navicularis fistula. No rectovesical,

rectoperineal or combined rectovaginal and rectovesical fistulas were encountered.

Five patients, or 33.3 per cent, had other associated congenital anomalies. These included absence of the gallbladder, horseshoe kidney, hydroureter and hydronephrosis, patent ductus arteriosus, anomaly of the ureters, hypospadias and unusually large foramen ovale and mongolian idiocy. The anomaly of the ureters was rather unusual. The ureters fused into one which emptied into the bladder on the right side, and the colon entered the bladder on the left side. In no instance was death directly attributable to any of the associated anomalies. All these associated congenital anomalies occurred in males with type 3 malformations.

SYMPTOMS

The symptoms presented by the patients varied with the type of anorectal anomaly and the presence or absence of associated fistulas.

Type 1.—The age range of patients with type 1 anomalies was from 6 weeks to 22 months, with an average age of $9\frac{1}{10}$ months. These patients never manifested symptoms of intestinal obstruction, although 1 of them became moderately distended, and were therefore seen later than those with other types of anomalies. The usual complaints were small, thin, frequent bowel movements associated with pain and crying. One child had liquid bowel movements and was found to have a fecal impaction. One mother noticed a small anal orifice. Another noticed some oozing from the rectum for three days after the child had been straining and having cramps with attempted bowel movement for four weeks.

Type 2.—Although no anomalies of type 2 were encountered in my patients, the symptoms expected from the pathologic observations and reported in the literature will be mentioned for the sake of completeness. The infants were usually seen within the first three days of life. The mother or the physician readily noticed the imperforate anus and the absence of meconium on the diapers. During the first thirty-six hours the absence of bowel movements was usually the only symptom, but after that period symptoms of intestinal obstruction appeared.

Type 3.—Of the 10 patients with type 3 anomalies, 7 were seen within the first two days of life, 2 were seen three and six weeks after birth respectively and 1 was seen ten months after birth. Four patients in the group had associated fistulas. The patient seen ten months after birth

had an adequate fistulous opening in the vagina through which the bowels moved, and she showed no evidence of intestinal obstruction. Three other patients had fistulas and were seen within the first two days of life. Two of these had adequate fistulous openings to permit the passage of fecal material and gas and therefore did not present symptoms of intestinal obstruction. The other one had a rectourethral fistula whose opening was evidently inadequate, because obstructive symptoms developed in a period of twenty-four hours.

There were 6 patients without associated fistulas in this group. Three of them presented definite symptoms of intestinal obstruction; 1 had a proctoplasty within twenty-four hours, before obstructive symptoms could develop, and 2 were seen three weeks and six weeks respectively after birth with double-barreled colostomies in the left lower abdominal quadrant.

Type 4.—Patients with type 4 anomalies are usually seen later than those with other types because the normal-appearing anus favors overlooking the possibility of a congenital anomaly. As a result, the intestinal obstruction which develops is of longer standing and the patients are more "toxic" and therefore poorer surgical risks.

PHYSICAL OBSERVATIONS

The observations on physical examination varied with the type of anorectal anomaly present and the age of the patient. The age is particularly important in the case of patients having a malformation which produces a complete occlusion of the anus or rectum. The patients acquire the signs characteristic of intestinal obstruction, namely abdominal distention, tympanites, intestinal patterning, increased borborygmi, vomiting and dehydration after twenty-four hours. Examination of the perineum will give one the information required to classify the type of anomaly and determine the presence or absence of a fistulous opening by observing the passage of fecal material or flatus from an abnormal site.

Type 1.—The anal opening ranged from 1 to 5 mm. in diameter, with an average diameter of 2 mm. One patient had an anal canal approximately 1 inch (2.5 cm.) long which admitted a fine probe. None of these patients had an obstruction higher in the anal canal. The colon in each patient was dilated and filled with fecal material. The external opening of a rectum-fossa navicularis fistula was observed in 1 patient.

Type 2.—In patients with type 2 anomalies the anal membrane is imperforate and discolored by the meconium. When the children strain or cry the impact of the meconium makes the membrane bulge.

Type 3.—Patients with this type of anomalies presented a variety of physical characteristics. The anal area had a dimple in 5 patients, and in the other 5 patients there was no ridge or dimple in the median raphe to denote the normal anal site. In 1 patient only was the blindly ending rectal pouch low enough to impart an impulse to the anal region on crying. In 2 male patients, meconium and gas were observed passing from the penile urethra. Two female patients had openings in the vagina through which fecal material was expelled. Three of the 4 patients had either a catheter or a probe inserted into the fistulous tract in an attempt to determine the position of the rectal pouch.

Type 4.—The anus is normal in appearance, but digital examination of the rectum reveals a complete obstruction within reach of the examining finger. The external sphincter is present and contracts on stimulation.

ROENTGENOGRAPHIC OBSERVATIONS

Roentgenographic studies of the intestinal tract were made for 9 of the 15 patients. Three in the group with type 1 malformation and 6 in the group with type 3 malformations.

The roentgenograms of the infants with type 1 anomalies revealed pronounced dilatation of the colon due to the gas and fecal material dammed back behind the constricted anus. These roentgenograms were merely flat plates of the abdomen for 2 patients and a flat plate made after the injection of a barium sulfate mixture in the form of an enema for the third patient.

Three different types of roentgenographic studies were utilized for the patients with type 3 anomalies. Of the 6 patients in this group, 1 had a series of roentgenograms of the gastrointestinal tract, 2 had barium sulfate mixture injected into the distal loop of the colostomy and 2 had flat plates of the abdomen in the upright and the inverted positions followed by a colostomy and subsequent barium studies of the distal loop of the colostomy. The purpose of these studies was to ascertain the position of the blind end of the sigmoid colon or rectum. Wangenstein and Rice⁷ advocated

the procedure of taking flat plates of the abdomen and pelvis with the child inverted and an opaque marker in the anal region. By this method the gas in the intestines will rise and fill the rectal pouch, giving an indication of its position with relation to the anal membrane. This procedure is of value only after twenty-four hours, when a sufficient amount of gas has formed to fill the intestines. Giving a barium meal for a series of gastrointestinal roentgenograms is contraindicated for these patients, just as for any other patient with intestinal obstruction.

TREATMENT

Treatment of congenital malformations of the anus and rectum also varies with the type of malformation present.

Type 1.—Of the 5 patients in this group, 3 were treated simply by rectal dilations. Of the other 2 patients, the one with a pinpoint opening had a simple proctoplasty which widened the anus so that the thumb could easily be inserted. The other patient had a rectum-fossa navicularis fistula with an orifice measuring 2 mm. in diameter. This patient was first seen when 19 months old and was treated by dilation of the orifice of the fistula and removal of a fecal impaction. This child was seen again when 2½ years of age, at which time a plastic operation was performed and the fistulous tract mobilized and placed in the proper position, with the opening at the normal anal site.

Type 2.—The accepted form of treatment for type 2 anomalies is simple cruciate incision of the anal membrane followed by anal dilations.

Type 3.—Treatment for persons with this type of anomalies was dependent on the presence or absence of obstructive symptoms.

Five patients had no obstructive symptoms and therefore had primary perineal operations. Four of these patients were operated on within the first two days of life and 1 after ten months, when she was first seen, with a recto-vaginal fistula through which the bowels moved. An incision was made in the midline, and the dissection carried upward, separating the transversus perinei and levator ani muscles. In 2 patients the rectum was penetrated and the peritoneum was opened accidentally. The wounds were packed, and the patients died twenty-four and thirty-six hours postoperatively with peritonitis. In the other 3 patients the rectum was mobilized and brought down to the skin incision, opened and then sutured to the skin edges. On 2

7. Wangenstein, O. H., and Rice, C. O.: Imperforate Anus—A Method of Determining the Surgical Approach, *Ann. Surg.* 92:77-81, 1930.

of these patients rectal dilation was done post-operatively starting ten days after operation. In 1 of these 2 patients an anal stricture developed; it was treated by a plastic operation and further dilation.

Five patients had obstructive symptoms and had sigmoid colostomies performed. One of these patients was first seen when 3 weeks old and another when 6 weeks old. Both had a sigmoid colostomy performed elsewhere when they were 2 days old. These patients had a perineal plastic operation as previously described. One died on the ninth postoperative day with peritonitis due to kinking of a loop of small intestine beneath the colostomy loop and resultant obstruction. The other died on the fifth postoperative day with a clinical picture of peritonitis. Two of these patients had primary sigmoid colostomies. One also had several inches of small intestine resected, followed by an antiperistaltic side to side anastomosis. This was done because of trauma to the small intestine and its mesentery. This patient died from shock on the day after operation. The other patient had a poorly functioning colostomy, and part of it became gangrenous and required excision. This patient had a rectourethral fistula, and pyelonephritis, which was fatal, developed. One patient had a colostomy performed when 1 day old and then had a perineal plastic operation (as described previously) approximately three months later. This patient subsequently died with a lobular pneumonia, urinary suppression and tubular nephrosis seven months after birth. At autopsy this patient also had a horseshoe kidney and absence of the gallbladder.

Type 4.—The accepted form of treatment for this type of anomalies is performance of a colostomy for relief of the intestinal obstruction, especially when the patient is in poor condition. The perineal rectal repair is then done later at a second operation. Usually the rectal pouch is high up in the pelvis and the perineal approach is difficult, requiring extensive perineal exploration. With the two sacs usually separated from each other, the lumens are usually joined by an oblique anastomosis.

The choice of anesthesia for infants is limited to use of either local anesthesia or drop ether. Drop ether was used in all the cases except 1 in which local anesthesia was used.

There was no mortality in patients with type 1 anomalies during their stay in the hospital. One patient died of pneumonia four months after

leaving the hospital. Until that time he was well and had good control of his bowels. The others are alive and well, with a normal-functioning anus, six months to six years after the operation. In the group with type 3 anomalies 7 of the 10 patients died during their stay in the hospital, a mortality of 70 per cent. Of the 3 patients who left the hospital alive, 2 are living and well four and five years after operation. One of the patients will have another operation to close a persistent rectovaginal fistula.

TABLE 3.—Mortality in This Study

Type of Anomaly	Males	Females	Total
1.....	0	0	0
2.....	0	0	0
3.....	7	0	7
4.....	0	0	0
Totals.....	7	0	7

At the present time, however, she has good control of her bowels, which move regularly, does not soil her clothes and does not pass feces from the vagina. A follow-up on the third patient that left the hospital alive was impossible, since both the physician and the surgeon who treated her are in the armed forces and the parents cannot be contacted. This patient was a mongolian idiot, and this condition in itself has a high mortality. It is probable that this patient is dead, since almost four years have elapsed since its birth. The average mortality for this

TABLE 4.—Mortality Reported in the Literature and in This Study

Type of Anomaly	Ladd and Gross		Crowell and Dulin		St. Mary's	
	Mortality, %	No. of Patients	Mortality, %	No. of Patients	Mortality, %	No. of Patients
1	9.5	21	0	3	0	5
2	16.6	6	4.3	6	No cases	
3	24.8	117	12.0	16	70	10
4	61.4	15	0	3	No cases	

series of patients was 46.6 per cent (tables 3 and 4).

Ladd and Gross⁴ reported a mortality of 9.5 per cent, 16.6 per cent, 24.8 per cent and 61.4 per cent in cases of type 1, 2, 3 and 4 anomalies respectively, the average mortality for the entire series being 28 per cent. Crowell and Dulin² reported a mortality of 17 per cent for 23 of the 28 patients treated surgically, 4.3 per cent and 13 per cent in cases of type 2 and type 3 anomalies respectively (table 4).

SUMMARY

Fifteen patients with congenital malformation of the anus and rectum were studied. In this group of patients only two of the four types of anomalies were represented. The treatment for the type 1 anomalies was satisfactory, but that for the type 3 anomalies was unsatisfactory, judging from the mortality in this group. Basically, the treatment was satisfactory in performing colostomies for patients with symptoms of intestinal obstruction and in attempting primary

perineal plastic operations for those patients free of obstructive symptoms. Two patients who had primary perineal operations died from peritonitis as a result of perforation of the rectum and contamination of the peritoneal cavity. These were technical accidents. The 5 patients presenting obstructive symptoms and for whom colostomies were performed died. One patient with a type 3 anomaly was given a barium sulfate meal as a diagnostic aid. This is contraindicated as for any other patient with intestinal obstruction.

ACUTE APPENDICITIS IN CHILDHOOD

H. WILLIAM SCOTT JR., M.D.

Junior Attending Surgeon, The Children's Hospital; Assistant in Surgery, Harvard Medical School
AND

PAUL F. WARE, M.D.

Resident Surgeon, The Children's Hospital; Assistant in Surgery, Harvard Medical School
BOSTON

In 1939 Hudson and Chamberlain¹ published statistics on 848 cases of appendicitis in patients treated at The Children's Hospital, Boston, during the ten year period preceding Jan. 1, 1939. Since that time there has been a significant decrease in the mortality of appendicitis in this clinic, and it is the purpose of the present study to evaluate the factors which are responsible for more successful therapy and to present an analysis of several aspects of the disease in childhood.

INCIDENCE

During the five and a half year period from Jan. 1, 1939 to June 30, 1944, there have been 506 children with acute appendicitis treated in this hospital. The various types encountered are listed in table 1.

TABLE 1.—Types of Appendicitis in 506 Children

Acute, unruptured without fluid.....	162
Acute, unruptured with fluid.....	119
Acute, ruptured with local peritonitis.....	96
Acute, ruptured with general peritonitis.....	90
Acute, ruptured with abscess.....	48

course of the disease in babies and young children than in persons in later life (table 2).

This is without question the age group in which early diagnosis is most difficult. It is interesting to note that in children under 6 years of age perforation was encountered more than twice as often as was simple acute appendicitis without rupture. All our patients under 2 years of age had perforated appendixes, with the single exception of an 11 month old boy who was operated on within twenty-four hours after the onset of symptoms.

There was no striking seasonal variation in the incidence of appendicitis in this five and a half year period.

TABLE 2.—Relation Between Type of Appendicitis and Age

Acute Unruptured		Acute Ruptured	
Age in Years	Number of Cases	Age in Years	Number of Cases
0-1	1	0-1	0
1-2	0	1-2	22
2-4	13	2-4	40
4-6	37	4-6	42
6-12	193	6-12	109
12-16	24	12-16	2

We have included in this series only proved cases of acute appendicitis with and without complication and have purposefully omitted all cases of appendectomy performed for other reasons.

Tabulation of sex incidence in this group of 506 cases reveals that 59 per cent of the patients were male and 41 per cent were female. This is in accord with the slightly greater predominance of males in most series of cases of adult patients.

Examination of the relation between type of appendicitis and age of our patients serves to support the view that perforation of the acutely inflamed appendix tends to occur earlier in the

ETIOLOGIC ASPECTS

It has long been felt that infections of the upper respiratory tract bear a definite relation to appendicitis and that the latter has its greatest incidence during the so-called "respiratory seasons." However, in our series infections of the respiratory tract were present immediately prior to hospitalization for appendicitis in only 16 per cent of cases, and this combination bore no relationship to a particular season of the year. According to Hudson and Chamberlain,¹ this figure represents the expected incidence of infections of the respiratory tract in the average child population.

The only acute illnesses other than infections of the respiratory tract preceding appendicitis in

From the Department of Surgery, Harvard Medical School, and the Surgical Service, the Children's Hospital, Boston.

1. Hudson, H. W., Jr., and Chamberlain, J. W.: J. Pediat. 15:408, 1939.

This group were gastroenteritis (10 cases), rheumatic fever (4 cases), bronchopneumonia (3 cases) and individual instances of mumps, whooping cough, bacillary dysentery and rheumatoid arthritis. The extremely low incidence of such diseases would seem to preclude any causal connection with appendicitis. A history of previous attacks of unexplained abdominal pain was elicited in 82 cases, an incidence of 16 per cent. While some of these episodes may have been acute appendicitis, our data are insufficient for definite conclusions. Pathologic examination of the appendix in these cases revealed old scarring in addition to the acute process in only a few instances. By and large, in this series acute appendicitis developed rather suddenly in children who had been previously well.

Wangensteen and colleagues² have recently produced the pathologic and clinical features of acute appendicitis experimentally in animals and in surgical patients. Their work seems to indicate that obstruction of the appendical lumen is the prime factor in the pathogenesis of the disease. They have shown that the appendix has a secretory function and that with obstruction it becomes analogous to a "closed loop." Continued secretion with obstruction may raise the intraluminal tension to the level of the systolic blood pressure. The anoxic appendical wall then provides an ideal medium for invasion by colonic bacteria in the secondary, or infective, phase of the disease.

Obstruction of the appendical lumen may be produced by several pathologic entities. Wangenstein,² was able to demonstrate the presence of Gerlach's mucosal fold in 80 per cent of over 500 cadavers and also, by microscopic study of the cecoappendical junction, the existence of a sphincter-like group of circular muscle fibers at the appendical base.

These two factors may possibly offer some resistance to the outflow of luminal secretions, but fecaliths appear to be the most positive cause of appendical obstruction. These concretions were found in 40 per cent of all appendixes in The Children's Hospital series on pathologic examination. In 66 per cent of specimens exhibiting perforation, fecaliths were present. The actual figure of incidence is probably much higher than this. Obviously, by the time of operation the fecalith may already have been extruded into the cecum or into the general peritoneal cavity through a perforation. Unfortunately, the

presence or absence of a fecalith in the peritoneal cavity has not been specifically recorded in most of the operative notes in our group of cases.

Another factor which may predispose to the development of acute appendicitis in children is infection of the appendix with pinworms (*Oxyuris vermicularis*). These parasites were present in the appendixes of 60 patients presenting the clinical picture of acute appendicitis in this five and a half year period. In 25 of these patients there was acute inflammation of the appendix, with perforations in 4 instances. The appendixes of the remaining 35 children, who had a typical clinical picture of appendicitis, showed no gross or microscopic inflammatory changes, and their cases are not included in this series. The relationship of pinworms to appendicitis was discussed by Botsford, Hudson and Chamberlain³ in 1939, but no definite conclusions as to etiologic connection could be formed. Nevertheless, it is possible that a bolus of pinworms may occasionally obstruct the appendical lumen in the same way as a fecalith does.

PATHOLOGIC SEQUENCES OF APPENDICITIS IN CHILDHOOD

With the establishment of obstruction of the appendical lumen the familiar changes of appendicitis take place in a well defined pattern. Increased intraluminal tension produces anoxia with edema of the mucosal layer and swelling of lymphoid follicles, frequently resulting in necrosis and ulceration of mucosa, especially at the points where follicles approach the surface. Bacteria present in the mucosa and luminal secretions may then penetrate the mucosal barrier, spreading readily in the loose submucosa and inciting a diffuse inflammatory process. The infection then passes through the muscularis along penetrating vessels and into lymphatics, as described by Aschoff,⁴ with further diffuse spread in the subserosal layer. Increased venous congestion results in transudation of fluid into the peritoneal cavity. This is enhanced by spread of inflammation to the serosal layer of the appendix and adjacent peritoneal surface, with the establishment of a periappendicitis. Perforation occurs with suppurative necrosis of the wall of the appendix or as a result of gangrene due to vascular thrombosis.

In general, it seems that this progression of changes leading to perforation is much more

2. Wangenstein, O. W.; Buirge, R. E.; Dennis, C., and Ritchie, W. P.: *Ann. Surg.* **106**:910, 1937. Wangenstein, O. W., and Dennis, C.: *ibid.* **110**:629, 1939.

3. Botsford, T. W.; Hudson, H. W., Jr., and Chamberlain, J. W.: *New England J. Med.* **221**:933, 1939.

4. Aschoff, L.: *Appendicitis*, London. Constable & Co., Ltd., 1932.

rapid in children than in adults. Of greater importance is the inadequacy of the "walling-off" mechanism in children with perforative appendicitis. In a child the appendix is usually longer in relation to the size of the peritoneal cavity and the cecum is frequently more mobile than in an adult. These two factors permit more widespread peritoneal contamination at the time of perforation. In addition, the omentum is frequently so short, so devoid of fat and so underdeveloped in early life that it offers little or no protection against spreading peritonitis of appendical origin. In older children, as in adults, the long, fatty omental apron usually serves to localize appendical peritonitis by adherence, thus

TABLE 3.—*Location of Pain in Relation to Type of Appendicitis*

Location	Acute Unruptured		Acute Ruptured	
	No. of Cases	Per Cent	No. of Cases	Per Cent
Periumbilical region.....	77	23.0	95	42.0
Right lower quadrant....	176	63.0	86	38.0
Generalized.....	8	3.0	44	18.0
Left lower quadrant.....	4	1.5	2	0.9
Lower portion of abdomen.....	7	2.5	3	1.3
Right upper quadrant....	1	0.4

forming a protective wall which inhibits diffuse peritoneal infection and facilitates the development of a local abscess.

DIAGNOSIS

Acute appendicitis is usually an easily recognizable clinical entity in later childhood, as the classic textbook features are commonly present. However, in infancy and early childhood this is unfortunately, not the case, and accurate early diagnosis may be extraordinarily difficult. Obviously, in dealing with such patients history can be obtained only from second-hand sources and is frequently of little help. The inability of an infant or young child to express clearly the presence of the pain of early appendicitis, together with misinterpretation of such manifestations of pain by parents, is likely to lead to serious delay in diagnosis. Fretfulness, irritability, refusal of feedings, disturbed sleep and screaming spells may be present for several hours before the parent becomes aware that the child objects to handling of the abdomen.

When pain can be accurately localized, it is most apt to begin around the umbilicus, with a later shift to the right lower quadrant of the abdomen on the development of periappendicitis. This sequence may be difficult to elicit, as children are frequently vague in describing their symptoms. With the development of peritonitis,

pain becomes generalized and severe. Table 3 compares the presenting location of pain at the time of hospitalization in simple and in perforative appendicitis.

Nausea and vomiting are constant symptoms in childhood appendicitis and usually occur subsequent to onset of pain. Only 13 children in this study failed to give a history of nausea. Vomiting occurred in 419 patients, an incidence of 83 per cent.

Temperatures of 100 to 101 F. usually accompany appendicitis in children and rarely exceed 102.6 F. except in patients with perforation and peritoneal involvement. Table 4 shows the relation between temperature and type of appendicitis in our patients.

The bowels are usually normal, but constipation prior to and during an attack of appendicitis is common, occurring in 26 per cent of these children. Diarrhea occurred in 83 children (16 per cent), almost all of whom had either spreading peritonitis or a pelvic appendicitis, most often with abscess, resulting in irritation of the sigmoid.

Urinary symptoms are uncommon, occurring in only 33 children in this group. Dysuria and frequency suggest that the inflamed appendix lies against the urinary bladder or over the right ureter. One child had grossly bloody urine associated with signs of appendicitis and at operation was found to have a perforated appendix localized by adherence to the dome of the bladder, with resulting secondary hemorrhagic cystitis.

TABLE 4.—*Relation Between Type of Appendicitis and Temperature*

Type	Temperature Range					
	Normal	100.5 F.	101.6 F.	102.6 F.	103.6 F.	104.6 F.
Acute unruptured....	52	116	63	29	8	1
Acute ruptured.....	10	36	61	62	46	16

Abdominal tenderness is the most consistent objective sign and unquestionably the most reliable one in the diagnosis of appendicitis, being absent in only 2 of these 506 patients. Maximal tenderness in the right lower quadrant of the abdomen was elicited in 385 children (76 per cent). In table 5 are listed the sites of tenderness in cases of simple and of perforated appendicitis.

Rectal tenderness was the second most common physical sign elicited in this series, being present in all but 15 cases of perforated appendicitis and absent in only 54 cases of simple acute appendicitis—a combined incidence of 87 per cent (table 6).

Involuntary spasm of the rectus muscle was found in 64 per cent of cases of unperforated and in 94 per cent of cases of perforated appendicitis (table 7).

We feel it important to stress that care and gentleness must be exercised to obtain satisfac-

TABLE 5.—*Site of Maximal Tenderness in 506 Cases of Appendicitis*

Location	Acute Unruptured, Number of Cases	Acute Ruptured, Number of Cases
Right lower quadrant.....	250	126
General.....	4	91
Lower portion of abdomen.....	8	12
Left lower quadrant.....	2	1
Right upper quadrant.....	...	2

tory information from the abdominal and rectal examination of sick and uncooperative children. Inspection alone will reveal a great deal to the observer during the all-important period spent in gaining the child's confidence. The usual order

TABLE 6.—*Location of Maximal Rectal Tenderness as Related to Type of Appendicitis*

Rectal Tenderness	Acute Unruptured, Number of Cases	Acute Ruptured, Number of Cases
Right.....	211	143
Right and left.....	6	73
Left.....	1	3
Not elicited.....	54	15

of physical examination from head to toes must be completely altered. The examiner should first turn to the abdomen, with emphasis on gentle palpation and unhurried movement from nontender points to suspected areas of tenderness. Dif-

TABLE 7.—*Spasm of Rectus Muscle in Simple and in Perforated Appendicitis*

Spasm	Acute Unruptured, Number of Cases	Acute Ruptured, Number of Cases
Right rectus.....	164	127
Generalized.....	7	89
Left rectus.....	3	3
Absent.....	99	14
Right rectus, upper half.....	...	1

ferentiation between voluntary and involuntary spasm in young children may be rather difficult. Considerable aid in this regard may be obtained by splinting the abdomen with the examining hand and allowing the latter to rest in one position for several minutes. After this maneuver,

if resistance of the rectus muscle persists, particularly during the inspiratory phase of respiration, peritoneal irritation may be diagnosed with accuracy, even for the most uncooperative child.

After completion of the general physical examination, digital examination of the rectum should always be performed. The well lubricated finger should slowly dilate the sphincter, and palpation of the pelvis should be deferred until the patient's cooperation is regained. Because of the child's small pelvis this maneuver, especially when combined with simultaneous abdominal palpation,

TABLE 8.—*Palpable Mass in 506 Cases of Appendicitis*

	Mass Palpated in 55 Cases by		
	Abdominal Examination Only, Number of Cases	Rectal Examination Only, Number of Cases	Combined Examinations, Number of Cases
Right lower quadrant.....	22	10	21
Left lower quadrant.....	1
Right upper quadrant.....	1

may reveal information not detected by abdominal examination alone. Indeed, a low-lying pelvic appendix and some appendical abscesses may be discovered only by this means (table 8).

A positive psoas sign was recorded in 63 cases in this series. Irritation of the psoas muscle may be readily apparent by a limping gait and the tendency of the child to lie with the right thigh partially flexed. Accessory methods of examina-

TABLE 9.—*Range of Leukocyte Count*

Leukocytes per Cu. Mm.	Acute Unruptured, Number of Cases	Acute Ruptured, Number of Cases
Under 10,000.....	25	17
10,000-15,000.....	86	59
15,000-20,000.....	89	61
20,000-30,000.....	50	82
Over 30,000.....	2	19

tion commonly used to elicit referred tenderness, such as cough and rebound tests, are of little value for young patients. Cooperation is difficult to obtain, and tenderness is almost inevitably referred to the area touched by the examiner.

A white blood cell count on admission of over 10,000 per cubic millimeter was encountered in 92 per cent of these 506 cases (table 9).

An elevation of polymorphonuclear leukocytes in the differential count was present even more consistently than was total leukocytosis (table 10).

It should be noted that in 17 children who had leukocyte counts below 10,000 perforation with peritonitis or abscess was present while 52 children without peritoneal involvement had a leukocyte count of over 20,000.

Some degree of ketosis, as manifested by acetoneuria, was almost invariably present in these patients. This can be related directly to the high incidence of nausea and vomiting in children with appendicitis and the rapid development of dehydration.

In the differential diagnosis of acute appendicitis in children one must adequately exclude gastroenteritis, constipation, nontuberculous mesenteric adenitis, acute pyelonephritis, bronchopneumonia and primary peritonitis. Rarely, acute rheumatic fever, acute poliomyelitis, diabetic coma and synovitis of the right hip may be confusing. In babies and young children intussusception and the symptoms of acute otitis media may occasionally be mistaken for appendicitis.

TABLE 10.—*Differential Count in Simple and in Perforated Appendicitis*

Per Cent of Polymorphonuclears	Acute Unruptured, Number of Cases	Acute Ruptured, Number of Cases
Under 70	13	5
70 to 80	47	35
85 to 90	76	74
Over 90	54	51

In general, abdominal pain, vomiting and slight fever should always be considered as due to acute appendicitis until proved otherwise. It is the policy of this clinic to hospitalize patients with these signs; repeated examinations are thereby facilitated, and an accurate early diagnosis can be made.

TREATMENT

There is little doubt that the treatment of acute unruptured appendicitis in children by immediate appendectomy is the procedure of choice. The management of early appendicitis is well standardized and offers no problem. The mortality rate of appendectomy for early appendicitis in most clinics approaches zero. However, for perforative appendicitis with peritonitis or abscess, mortality rates remain distressingly high, particularly in children. The inadequacy of localizing factors in children with perforative appendicitis, resulting in diffuse peritoneal contamination, makes appendectomy imperative as soon as the patient's condition permits in order to remove the source of infection. Delayed operation, or Ochsnerization, results in death from peritonitis before a localized abscess can be formed in a

prohibitively high percentage of cases in childhood. Conversely, if early operation is employed for children with appendical peritonitis without adequate preoperative preparation, many unnecessary deaths occur from toxemia.

It is the policy of this clinic⁵ to individualize the preparation of children with appendical peritonitis or abscess for operation, delaying appendectomy only for the brief period necessary to obtain the maximum benefit of supportive measures. For children with localized peritonitis or abscess this may be only a matter of three to six hours, but for the severely ill, extremely toxic children with neglected general peritonitis, frequently twelve to eighteen and occasionally twenty-four hours of supportive therapy are indicated before appendectomy is justified.

Since dehydration and ketosis are so common, even in children with early appendicitis, preoperative intravenous administration of dextrose in isotonic solution of sodium chloride is almost routine in this clinic. For the seriously ill children with peritonitis a constant intravenous drip is instituted for the infusion of plasma, as well as dextrose and saline solutions. Sodium sulfadiazine is given parenterally in an initial dose of $\frac{1}{2}$ grain (0.03 Gm.) per pound (0.5 Kg.) of body weight. Fowler's position, constant gastric suction by the Wangenstein method, morphine in three to four hourly doses and high concentration (95 per cent) oxygen complete the therapeutic regimen.

The decision as to time for operation in these cases is based on the response of the patient to this therapy with improvement in his clinical status as evidenced by his general appearance, a significant reduction in temperature and, of greatest importance, a 20 to 30 per minute decrease in pulse rate with improvement in its quality (see chart).

Although most of our patients with peritonitis responded satisfactorily to these supportive measures in six to twelve hours, a few have shown little change in their extreme toxicity even after twenty-four hours of treatment. When one is faced with this problem, considerable clinical judgment is required, and it is essential to recall that removal of the ruptured appendix offers the child the greatest assistance in overcoming his infection. However, in rare cases the moribund state of the child may preclude any more extensive procedure than simple incision and drainage of the abdomen under local anesthesia. While this procedure is not ideal.

5. Ladd, W. E., and Gross, R. E.: *Abdominal Surgery of Infancy and Childhood*, Philadelphia, W. B. Saunders Company, 1940.

the temporary avenue of escape which it offers to peritoneal exudate is of far greater advantage in young patients than is prolonged Ochsnerization alone.

All the 506 patients with acute appendicitis observed in The Children's Hospital between January 1939 and July 1944 were operated on. The appendix was removed at the initial operation in 472 cases (93 per cent), while in 34 cases (7 per cent) it was deemed inadvisable to do more than incision and drainage. Of these patients 30 were later admitted for interval appendectomy.

The choice of incision for appendectomy in children depends on the size of the child and the type of appendicitis. Because of the small area which presents between the linea semilunaris and the anterior superior iliac spine in young children, the McBurney incision may give inadequate exposure, particularly of pelvic appendices. In

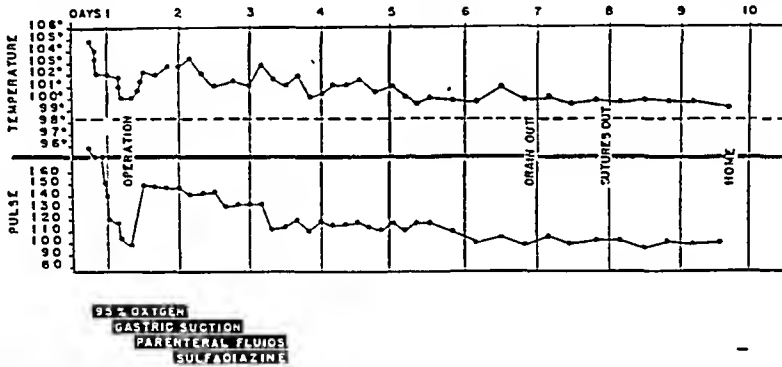
suture of silk, except in the presence of an edematous, markedly inflamed and friable cecal wall.

We feel that drainage of the pelvis has a distinct usefulness for children with peritonitis of

TABLE 11.—Types of Incision Used in 506 Cases of Appendicitis

Incision	Number of Cases
Right rectus, lateral retracting.....	205
McBurney.....	120
Right rectus, medial retracting.....	100
Rectus splitting.....	78
Rockey.....	1
McBurney, left.....	1
Left rectus, medial retracting.....	1

appendical origin. There has been considerable argument in surgical literature between the proponents of peritoneal drainage and the opponents of this practice, beginning with the work of Yates⁶ in 1905. In recent years there has been a



Clinical course of a case of severe appendical peritonitis. The patient was a 24 month old child weighing 24 pounds (10.9 Kg.).

this clinic use of this incision is largely restricted to older children with early appendicitis and well localized tenderness of the right lower abdominal quadrant or retrocecal appendicitis and as a means of extraperitoneal drainage of an appendical abscess.

The right rectus incision gives excellent exposure of the appendix in children with minimum retraction. Retraction of the rectus muscle is preferable to splitting of the belly of the muscle, since it insures a stronger wound. As medial retraction easily damages the nerve supply of the muscle, we have recently employed lateral rectus retraction almost exclusively. If drainage is indicated, the tubing may be led out through a stab wound in the lower portion of the belly of the rectus muscle. Types of incision used in this series are recorded in table 11.

It is the policy in this clinic to invert the appendical stump into the cecum with a purse string

distinct trend toward the more infrequent use of drains, particularly since the advent of chemotherapy. While it is admittedly impossible to drain the entire peritoneal cavity, except temporarily, it is the opinion of this clinic that a drain left in the pelvis in cases of appendical peritonitis has two distinct advantages: 1. It allows a temporary means of escape of exudate whose absorption would mean more fever and toxicity in the immediate postoperative period. 2. A sinus is formed into which local collections of pus in the pelvis or iliac fossa may subsequently rupture or be evacuated, and thus additional operative procedures and delayed convalescence can be avoided. In table 12 the operative procedures employed in the 506 cases are listed.

The use of intraperitoneal drains has been opposed by many authors on the ground that drainage increases peritoneal adhesions and con-

6. Yates, J. L.: Surg., Gynec. & Obst. 1:473, 1905.

sequently results in a greater incidence of intestinal obstruction following peritonitis. While we do not deny this possibility, our experience has not confirmed it, and we feel that other factors are more significant in this regard. Among these must be listed operative trauma to visceral and parietal peritoneum (rough handling, glove powder, heavy retraction, dry gauze and so forth) and localized intraperitoneal abscesses. The incidence of the latter is reduced by a thorough aspiration of pus at the time of operation, gently separating fibrinous adhesions by the wet, gloved finger so as to release pocketed exudate for removal by suction. In this clinic we use soft, pliable rubber drains with a central core of gauze (Penrose). The drain is always led down into the pelvis along its lateral wall and should never be placed among loops of bowel or against the appendical stump.³ Although we have tended to use drainage less often in recent years, we feel that results obtained in the treatment of

azine in reducing the incidence of these complications.

TABLE 13.—Postoperative Abscesses in Relation to Treatment

Operative Procedure	Pelvic Cases	Wound Abscess	Subdiaphragmatic Abscess
Appendectomy.....	273	—	2
Appendectomy with drain.....	23	5	..
Appendectomy with local and/or parenteral sulfonamide therapy.....	26	4	3
Appendectomy with drain and parenteral sulfonamide therapy.....	97	17	6
Appendectomy with drain and local and parenteral sulfonamide therapy.....	73	6	5
Incision and drainage with parenteral and/or local sulfonamide therapy.....	29	2	1
Incision and drainage.....	5
Totals.....	566	34	17

When a well localized appendical abscess presents as an abdominal mass at the time of hos-

TABLE 12.—Operative Procedures Employed for Various Types of Appendicitis

Type	Appendectomy, Number of Cases	Appendectomy with Drain and Sulfonamide Compound Locally, Number of Cases	Appendectomy with Drain, Number of Cases	Incision and Drainage, Number of Cases	Appendectomy with Sulfonamide Compound Locally, Number of Cases
Acute unruptured.....	247	6	13	..	6
Acute ruptured with peritonitis.....	6	61	106	11	5
Acute ruptured with abscess.....	1	6	18	23	..

pendical peritonitis in this hospital offer substantial support to the rationale of this mode of crapy.

Intraperitoneal administration of sulfonamide compounds was used in 72 appendectomies for perforative appendicitis with abscess or peritonitis. In 67 of these cases a drain was also employed. Sulfadiazine was used in 50 cases, sulfanilamide in 17 and sulfathiazole in 5. Five patients with ruptured appendixes were treated by appendectomy with intraperitoneal applications of a sulfonamide compound and no drainage, and 6 by appendectomy with no local drug or drain. All these 11 patients received additional chemotherapy orally and/or parenterally in the postoperative period.

In table 13 we have tabulated the postoperative wound infections and postoperative peritoneal abscesses which have been encountered in this series. While no definite statistical conclusions can be drawn from these figures, it seems that in our cases the intraperitoneal use of sulfonamide compounds offered no great advantage over the oral or parenteral use of sulfathiazole or sulfadi-

pitalization, direct drainage should be employed whenever possible. Incision should be centered over the presenting mass and the abscess entered directly without an opening into the uncontaminated peritoneal cavity. This may usually be accomplished through a McBurney incision, but in a few instances the position of the abscess may be such that a rectus incision offers a more direct approach. The appendix is removed if easily available, and the cavity is drained. However, when the appendix is incorporated in the wall of the abscess and cannot be removed without destruction of the inflammatory barrier, with subsequent generalized peritoneal infection, simple drainage should be instituted and appendectomy deferred for about six months.

The postoperative period following appendectomy for acute nonperforative appendicitis in children presents few problems. We have used chemotherapy postoperatively only when smears or cultures of the peritoneal fluid taken at operation have revealed organisms. By the routine use of Wangenstein's gastric suction for six to twelve hours after operation vomiting and the

associated danger of aspiration in young children may be successfully obviated.

The importance of a well planned postoperative regimen for children with appendical peritonitis cannot be overemphasized. Rest for the patient and, insofar as possible, for the gastrointestinal tract is essential for resolution of peritoneal inflammation. Morphine is given in adequate doses every three to four hours. Constant gastric siphonage by the Wangenstein method with an inlying Levine tube in older children or a urethral catheter in babies should be used routinely to prevent nausea, vomiting and the distention of adynamic ileus. Miller-Abbott tubes are usually not necessary and because of their size have a limited usefulness for children. Fluids for parenteral administration are best given by a constant intravenous drip through a 19 or 20 gage needle, which will usually be tolerated for eighteen to twenty-four hours without danger of thrombophlébitis. Occasionally it may be necessary to cannulate a vein directly. It is our feeling that bone marrow infusions, with their inherent danger of osteomyelitis, periosteal stripping and subsequent sequestration, should rarely be used. Marrow infusions are advocated chiefly for children under 2 to 3 years of age, but we feel that it is safer and simpler to give repeated infusions by scalp veins in this age group, short-beveled 24 gage needles being used and the fluid administered under slight pressure. Solutions of 5 or 10 per cent dextrose in water or isotonic solution of sodium chloride are used most commonly in combating the ketosis, dehydration and fluid losses in these children.

Precautions must be observed to avoid overloading the child with excessive saline solutions. An amount of isotonic solution of sodium chloride may be given roughly corresponding to Wangenstein drainage; but if prolonged suction is required, determinations of blood chloride and serum protein levels are necessary to indicate more accurately the type of fluid required. Infusions of plasma are indicated for hypoproteinemia and transfusions of whole blood if there is anemia as well. It is felt that repeated small transfusions of fresh whole blood are helpful for critically ill children with peritonitis. If suction and parenteral administration of fluids are necessary for more than two or three days, solutions of amino acids should be added to the parenteral feeding regimen. By this means, protein deficiency from inadequate intake and loss in peritoneal exudate may be compensated.

It is important to maintain a strict chart of intake and output in order to regulate fluid

balance. Daily requirements for parenterally administered fluids average 2.5 to 2 ounces (75 to 60 cc.) per pound (0.5 Kg.) for babies under 2 years and 1.5 ounces to 1 ounce (45 to 30 cc.) per pound for children over 2 years of age.

Chemotherapy was administered postoperatively in 87 per cent of the cases of perforated appendicitis in this series. Sulfathiazole was used in 82 cases and sulfadiazine in 99. Both drugs seemed effective in diminishing postoperative toxicity, shortening convalescence and reducing complications, but fewer reactions to the drug were encountered with sulfadiazine. Sodium sulfadiazine should be administered subcutaneously or intravenously in doses of $\frac{1}{2}$ to $\frac{3}{4}$ grain (0.06 to 0.09 Gm.) per pound per day until gastric suction is discontinued, when the drug is given by mouth. It is our practice to continue chemotherapy for these children after operation until all signs of infection have abated, as evidenced by a normal clinical chart and white blood cell count, a cessation of discharge from the drain sinus and negative results of rectal examination.

We have routinely employed Fowler's position for all patients with peritonitis in this series and feel that it is helpful in evacuating exudate when drainage has been used. Despite certain theoretic objections to the usefulness of this position in enhancing the pelvic localization of exudate, it is interesting to note that in only 3 cases did subdiaphragmatic abscess occur in our patients. Ninety-five per cent oxygen has been found extremely useful for children with diffuse peritonitis as a means of preventing or of reducing the distention of paralytic ileus. Hot abdominal poultices and rectal tubes have been used routinely at two to three hourly intervals in the postoperative period for a similar purpose. Heat to the abdomen probably has its greatest benefit in increasing the patient's comfort and decreasing the incidence of infection in the wounds.

In table 14 we have compiled statistics on postoperative treatment in our cases of appendical peritonitis or abscess. These show a trend toward a more standardized regimen in recent years.

COMPLICATIONS

The various complications encountered in these 506 cases are listed in table 15. Pelvic abscess was the most common postoperative complication, occurring in 12 per cent of the 234 cases of perforating appendicitis in this series. In no instance was operative drainage of a pelvic abscess required. Treatment consisted in the resumption of chemotherapy if this had been discontinued and the use of hot rectal irrigations.

With this regimen 2 abscesses drained spontaneously by rectum, while the remainder were either resorbed or evacuated via the drain sinus. There was no mortality in this group. We have been unable to find in the literature a comparable

perforated appendicitis. In 17 cases this complication appeared during the first or second week after operation, while in 2 cases late obstruction occurred five and twelve months respectively following peritonitis. Early intestinal obstruction

TABLE 14.—*Postoperative Treatment of Perforated Appendicitis*

Year	Total No. of Cases	Falls Parenterally		Sulfonamide Compounds		Suction		Oxygen (95 per Cent)	
		No. of Cases	Average Duration, Days	No. of Cases	Average Duration, Days	No. of Cases	Average Duration, Days	No. of Cases	Average Duration, Days
1929	27	24	4	4	4.7	19	2	9	3
1930	20	20	6.5	25	9	27	4	11	3.3
1931	15	16	4	15	6.1	42	3.2	20	1.7
1932	14	14	3	17	12	42	2	6	1.7
1933	34	27	2	20	8	52	3	7	2.4
1934	20	20	2.3	20	10.2	19	2.6	3	2.6

TABLE 15.—*Postoperative Complications in Relation to Type of Appendicitis*

Complication	Acute Unruptured, Number of Cases	Acute Ruptured, Number of Cases	Operative Treatment, Number of Cases
Perforated abscess	4	20	None
Intestinal obstruction	3	17	12
Pneumonia	2	15	None
Wound abscess	5	12	6
Fecal fistula	1	3	None
Contagious disease	1	1	None
Evisceration	None	3	5
Atelactasis	1	None	None
Bacteremia	1	2	None
Hilar abscess	None	2	2
Pyelonephritis	1	1	None
Wound fistula	None	2	2
Subphrenic abscess	None	2	None
Pyrexia convulsions	None	1	1
Peritoneal abscess	1	None	None
Thrombophlebitis	1	1	None
Myocardial failure	None	1	None

tion is usually a result of friable, fibrinous adhesions due to a plastic exudate between loops of bowel. In the earlier cases of this series Witzel enterostomy was usually done without delay, but this has been rarely necessary in recent years. Resorption of exudate with relief of the obstruction will take place in most instances within a few days if decompression of the distended bowel is accomplished by constant gastric siphonage or the use of a Miller-Abbott tube. High concentration oxygen is also of definite value in this regard. For late intestinal obstruction laparotomy and lysis of adhesions is clearly indicated. In table 16 we have recorded the time of onset and type of treatment used in the cases in this

TABLE 16.—*Time of Onset and Treatment of Intestinal Obstruction*

Patient	Year	Type of Appendicitis	Onset of Obstruction (Post-operative)	Treatment	Result
1	1929	Perforated, with general peritonitis	5 days	Witzel enterostomy	Well
2	1929	Perforated, with general peritonitis	5 days	Witzel enterostomy	Well
3	1929	Perforated, with abscess	3 days	Witzel enterostomy	Well
4	1929	Perforated, with abscess	9 days	Lysis of adhesions and Witzel enterostomy	Well
5	1929	Acute, unruptured	5 days	Witzel enterostomy	Well
6	1929	Perforated, with general peritonitis	5 days	Witzel enterostomy	Well
7	1929	Perforated, with general peritonitis	5 days	Miller-Abbott suction (5 days)	Well
8	1930	Perforated, with abscess	3 days	Miller-Abbott suction 5 days, then lysis of adhesions	Well
9	1930	Acute, unruptured	11 days	Gastric suction (3 days)	Well
10	1930	Perforated, with general peritonitis	12 days	(a) Witzel enterostomy	Well
11	1931	Acute, unruptured	(a) 9 days	(b) Lysis of adhesions	Well
12	1931	Acute, unruptured	(b) 5 mo.	Suture of eversion; lysis of adhesions	Well
13	1931	Perforated, with local peritonitis	5 days	Gastric suction (3 days)	Well
14	1931	Perforated, with local peritonitis	5 days	Gastric suction (3 days)	Well
15	1931	Perforated, with abscess	11 days	Gastric suction (3 days)	Well
16	1931	Perforated, with abscess	17 days	Lysis of adhesions	Well
17	1931	Perforated, with local peritonitis	12 mo.	Incision and drainage of abscess; Witzel enterostomy	Well
18	1931	Perforated, with local peritonitis	On admission	Gastric suction (1 day)	Well
19	1931	Perforated, with local peritonitis	16 days	Miller-Abbott suction (10 days)	Well
20	1931	Perforated, with local peritonitis	7 days	Miller-Abbott suction (10 days)	Well

group of cases of appendical peritonitis treated without drainage in which figures on this complication were listed, but we feel that our experience in this regard illustrates the value of drainage.

Intestinal obstruction was encountered subsequent to operation in 7.3 per cent of the cases of

series in which intestinal obstruction developed. No deaths occurred as a result of this complication.

The secondary operations which were performed in this entire group of 506 cases are listed in table 17. An effort was made to readmit every child who had simple drainage of an

appendical abscess or of an overwhelming appendical peritonitis without appendectomy about six months after the initial illness for interval appendectomy.

MORTALITY

There were 8 deaths in this series of 506 cases, an over-all mortality rate of 1.58 per cent. Only 1 death occurred in the 272 cases of acute unruptured

TABLE 17.—*Secondary Operations in 506 Cases of Appendicitis*

Operative Procedure	Number of Cases
Interval appendectomy.....	30
Witzel enterostomy.....	8
Lysis of adhesions.....	4
Drainage of wound abscess.....	6
Drainage of subphrenic abscess.....	3
Drainage of retroperitoneal abscess.....	1
Drainage of iliac abscess.....	2
Suture of eversion.....	3
Incisional herniorrhaphy.....	2

tured appendicitis. This patient was a 10 year old Negro boy who had symptoms of abdominal pain, chills and swinging fever for nine days before operation. An acutely inflamed, unruptured appendix was found in a high retrocecal position with no peritonitis but with well established pyelephlebitis. The postoperative course was extremely stormy, with daily rises in temperature to 105 to 107 F., and the child finally died on the forty-fifth day in the hospital.

TABLE 18.—*Relation of Age of Patient and Type of Appendicitis to Mortality*

Total cases in series, 506; over-all mortality rate, 1.55 per cent.

Age Group, Years	Acute Unruptured Appendicitis			Acute Ruptured Appendicitis		
	Number of Cases	Deaths	Mortality, per Cent	Number of Cases	Deaths	Mortality, per Cent
0-1	1	0	0.0	0	0	0.0
1-2	0	0	0.0	22	3	13.6
2-4	15	0	0.0	59	3	5.1
4-6	37	0	0.0	42	0	0.0
6-12	193	1	0.5	109	1	0.9
12-16	24	0	0.0	2	0	0.0
Total	272	1	0.36	234	7	2.99

The 7 deaths in our 234 cases of perforated appendix all occurred in children with generalized peritonitis—a mortality rate of 2.99 per cent. Four of these children had pneumonia in addition to peritonitis. Two other patients died with "ether convulsions" and hyperpyrexia immediately after operation. In retrospect, in neither of these cases had there been adequate preoperative preparation, and both children were operated on

while they were under ether anesthesia and had temperatures over 104 F. and pulse rates over 150. With adequate preoperative preparation, these deaths might easily have been prevented. The last fatality occurred in a child in whom a bacteremia due to *Bacillus coli* developed after appendical peritonitis with a terminal *B. coli* endocarditis.

TABLE 19.—*Relation Between Duration of Symptoms and Type of Appendicitis*

Duration of Symptoms	Acute Unruptured Appendicitis	Acute Ruptured Appendicitis	Incidence of Perforation, per Cent
0 to 12 hours	67	2	3
12 to 24 hours	116	25	21
24 to 36 hours	28	28	50
36 to 48 hours	24	41	64
2 to 3 days	11	19	65
3 to 4 days	14	34	70
4 to 5 days	5	11	79
5 days and over	7	61	90

TABLE 20.—*Duration of Symptoms in Relation to Mortality*

Duration of Symptoms Before Operation	Cases	Deaths	Mortality, Percentage
0 to 12 hours.....	69	0	0.00
12 to 24 hours.....	152	1	0.65
24 to 36 hours.....	56	0	0.00
36 to 48 hours.....	67	1	1.49
2 to 3 days.....	30	2	6.66
3 to 4 days.....	43	1	2.33
4 to 5 days.....	16	1	6.25
5 days and over.....	63	2	3.17

TABLE 21.—*Relation Between Type of Appendicitis and Mortality Rate of the Children's Hospital, Boston, from 1928 to 1939 and from 1939 to 1944*

Type of Appendicitis	Cases	Deaths	Mortality, Percentage
1928 to 1939			
Acute, unruptured.....	475	2	0.42
Acute, ruptured with local or diffuse peritonitis.....	373	24	6.43
Totals.....	848	26	3.05
1939 to July 1944			
Acute, unruptured.....	272	1	0.36
Acute, ruptured with local or diffuse peritonitis.....	234	7	2.99
Totals.....	506	8	1.58

In table 18 we have presented the relation between age of patient, type of appendicitis and mortality rate in our patients. For children under 4 years of age, the mortality rate was 6.2 per cent, as compared with 0.48 per cent for children over 4 years. This discrepancy must be attributed to the more rapid development of generalized peritonitis and to the greater difficulty encountered in making early diagnosis for the younger children.

The relation between duration of symptoms and type of appendicitis is recorded in table 19. In table 20 the duration of symptoms is compared with the mortality rate. It is discouraging to realize that almost one fourth of our patients were hospitalized only after three days or more of symptoms. This represents the same proportion of cases of neglected appendicitis that was encountered in the children with appendicitis treated in this clinic between 1928 and 1939 and would seem to indicate that there has been no advancement in the early recognition of the disease in children by practitioners or by the lay public.

A comparison of mortality rates in the present series and those of the preceding ten year period is presented in table 21. It is interesting to note that the over-all mortality rate has been reduced by approximately 50 per cent and that the recent

percentage of fatalities in cases of perforated appendicitis is actually lower than the over-all rate of the earlier group of patients.

It seems apparent that the accomplishment of improvement in the treatment of appendicitis, particularly of the perforative type, must be attributed to multiple factors and not merely to the use of sulfonamide drugs. These factors include more adequate preoperative preparation; early appendectomy, as soon as general toxicity is reduced; a better standardized postoperative regimen, including routine gastric suction, Fowler's position and parenteral administration of fluids, with the addition of sulfadiazine in cases of perforation. As a result of these factors, no deaths occurred in this clinic in 236 cases of appendicitis during the last three years of this observation.

SURGICAL TREATMENT OF LYMPHEDEMA

J. L. RANSOHOFF, M.D.

CINCINNATI

The question of the treatment of elephantiasis has been a puzzling one for many years. The decision as to method is not greatly influenced by consideration of the etiologic factors of the disease, which is always due to an obstruction of the normal lymph channels and subsequent swelling of the extremity. For the purpose of classification, lymphedema may be stated to be due (1) to filariasis; (2) to inflammatory or scar tissue obstructing the normal lymph channels, as occurs commonly after radical operations on the breast, and (3) to some obscure lesion that obstructs the lymph channels. The last, which may be called idiopathic, is a very small class. The kind following phlegmasia alba dolens is not considered here, as this is far more venous than lymphatic in origin.

The problem of surgical treatment in cases of lymphedema has long taxed the ingenuity of surgeons. The subject assumes greater importance with the possibility of a large number of cases occurring in our troops in the tropical theaters of war. Several operative procedures have been suggested and tried. The Kondoleon operation has had the greatest vogue and has given more or less indifferent results. The Kondoleon operation, if done properly, is an operation of considerable magnitude. With the meager results so far obtained, it is doubtful whether this operation has great applicability.

An operation suggested by Handley¹ in 1908 should be given further trial. The principle is to bury long silk sutures in the edematous area to serve as permanent lymph channels and to conduct the lymph away from the infected area to normal lymph channels.

Recently I have used a modified Handley operation in 2 cases, and the results were gratifying. The result in the first case is startling.

REPORT OF CASES

CASE 1.—A nurse, aged 24, six months before she consulted me, while at work, suddenly noticed a swelling of the left hand, without injury and with no sensation of pain. This swelling increased in size, until it looked as though she were wearing a boxing glove on the left hand. She had been to various clinics in an attempt to

remedy this condition. Her treatment had included massage and rest in bed, with elevation of the hand. An attempt was made to block the brachial plexus, with the idea that it was of neurogenic origin. Another attempt was made to inject the brachial artery, with the idea that there was some arterial disease. The swelling of the hand was so great that there was practically no motion of the fingers, and the roentgenogram showed atrophy of all the bones of the hand. The patient had lost 50 pounds (22.7 Kg.) and was in a state of extreme depression.

On Sept. 26, 1944 a modified Handley operation was done. Double strands of no. 1 nylon were used in

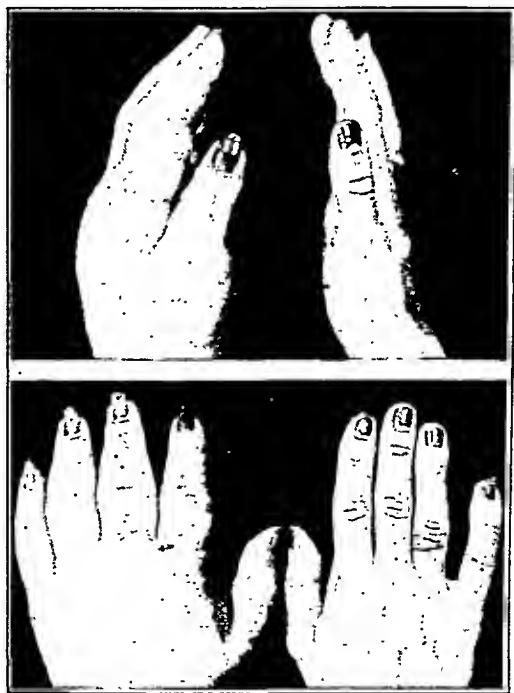


Fig. 1 (case 1).—Normal and abnormal hand before operation. A, lateral view; B, dorsal view.

place of silk, as it was thought that this would be less irritating and remain in the tissues indefinitely. A small transverse incision, which can be seen in the photograph, was made just distal to the first phalanx of the ring finger, and through a specially constructed long probe, the suture was passed through several small incisions, under the superficial fascia, to the normal areolar tissue in the cubital fossa. The small incisions were closed with fine silk. On the day following the operation, it was apparent that the swelling, not only of the ring finger but of all the fingers, had begun to recede, and six weeks later the hand was apparently normal. At no time was there secretion from the wounds. After the

1. Handley, W. S.: Lymphangioplasty, *Lancet* 1: 783, 1908.

disappearance of the swelling, the function of the hand was improved by physical therapy. Within two months the hand was completely normal.

At present, seven months after operation, the patient is back at work as a nurse and has made application to join the Navy; she has been assured by the medical examiner that she will be accepted.

of sutures were used, one anterior and one posterior, the posterior extending from the wrist to the subscapular fossa and the anterior extending from the wrist to the normal areolar tissue over the sternum. The improvement was almost immediate. At the time of writing, one month after operation, the woman has



Fig. 2 (case 1).—Dorsal view of both hands about four weeks after operation.

CASE 2.—A 63 year old woman was operated on eight years ago for carcinoma of the left breast. The operation was followed by edema of the left arm, which increased in severity. At the time of examination the arm was almost useless, because of the indurated, brawny skin, which had marked pigskin dimpling. She could not raise her arm above the angle of 33 degrees, nor could she completely flex her elbow.

On March 22, 1945, an operation was performed according to the same technic. In this case, two sets

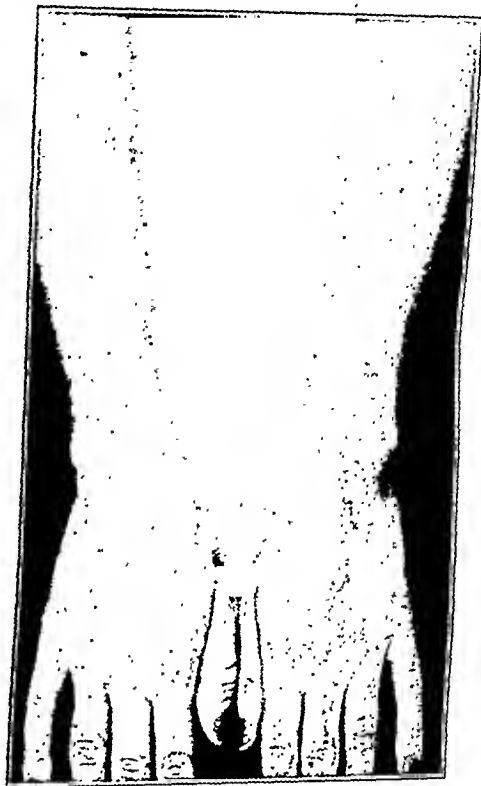


Fig. 3 (case 1).—Dorsal view of both hands six months after operation.

complete use of her arm and the skin has become soft and pliable. At the time of operation, the involved arm was $1\frac{1}{2}$ to 2 inches (3.8 to 5 cm.) greater in girth measurement both in the forearm and in the upper arm than the other arm; at present the measurements of the two arms are the same.

INTERNAL DERANGEMENTS OF THE KNEE JOINT

MAJOR RUSSELL F. JAEKLE

MEDICAL CORPS, ARMY OF THE UNITED STATES

This paper reports a consecutive series of 190 arthrotomies of the knee joint done on military personnel in the Station Hospital, Camp Roberts, Calif., within a two year period. The patients operated on were in one sense selected, because operation was not advised or done if it appeared that the patient was unstable and had not the will to get well. At least an equal number of patients with affected knee joints were not operated on and have since been reclassified or discharged from service. Many of these patients had deranged joints before their entry into service and had been advised by their own physicians not to have operations. It is amazing how widely the misunderstanding has been implanted that "if the joint is opened and the water runs out the knee will be dry and stiff."

In this series the follow-up is incomplete but for practical purposes it is sufficient to permit estimation of definite results. None of the patients were seen more recently than six months before the time of writing. When the training period of three or four months is completed in Camp Roberts, the soldiers are usually moved to another camp, although many are retained for much longer periods. When a man has lost time during the training cycle, he is put into another unit and goes through the complete course, in some cases repeating part of the previous training. Almost without exception the follow-up period is at least three months, with the soldier doing the same regular duty as the other, normal men. The patients for whom reclassification was necessary will be considered later under analysis of specific types of injuries. Many patients have been followed for one year or more in this camp and through reports from other hospitals and letters. Some men have written from overseas.

DIAGNOSIS

The subject of diagnosis is so well covered in the various textbooks and journals that further comment is superfluous, except a caution against the asking of leading questions when the examiner is taking a history. The patient should be allowed to tell his own story and should always be given a choice in answering; that is, the examiner should ask, "Do you have trouble in bending

or straightening the knee, or what is the difficulty?" Many patients say that the knee is "locked," but it is found with questioning that motion was not blocked at all until severe swelling occurred. A point to emphasize is that in case of acute injury the roentgenogram appears normal. One should never tell the patient that the knee has no internal articular injury because the roentgenogram is normal. If the history and examination are otherwise indicative of injury, operation should be done, and the surgeon should not be content with simple inspection of the opened joint. Gentle traction on the cartilage or exploration with a blunt hook usually demonstrates a posterior tear. Mistaken diagnoses will be made in any series of cases. In 6 cases of the present series there was no tear of cartilage but the patients had hypertrophic fat pads, which required excision.

TABLE 1.—*Analysis of One Hundred and Fifty-Five Cases of Torn Cartilage*

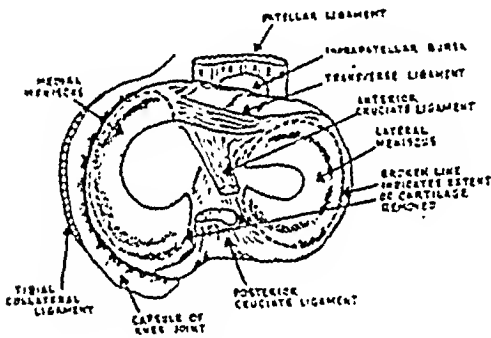
Type of Tear	Location of Tear		
		Medial	Lateral
Anterior.....	16		
Posterior.....	24	Right..... 79	2
Bucket handle.....	50	Left..... 69	5
Lateral.....	29	—	—
Transverse.....	6		145
	155	Lateral tears constitute 4.73 per cent of the total number.	

TREATMENT

In all cases the patient was taught exercises for the quadriceps muscle before the operation and was impressed with the idea that his cooperation was the deciding factor in a successful operation. In cases in which the patient exercises well after operation, the normal physiologic action is maintained and he does not suffer weakness and relaxation of the knee. One preparation of the skin is done on the day before the operation, and the whole extremity is wrapped in sterile towels. Another preparation is done while the patient is on the table. Spinal anesthesia is used in all cases. The legs hang over the end of the table with the knees at a right angle. The operator sits on a stool and the leg to be operated on can be grasped by the surgeon's own knees; this permits traction and rotation of the leg as desired.

This position is a great help in exposure of the joint and also obviates the need for one assistant. The short straight parapatellar incision is used and provides good exposure. In 3 cases, bucket handle tears of both medial and lateral menisci in the same knee were removed easily through one incision. If the lower pole of the incision does not sever the inferior medial articularis genu artery, there is much less postoperative swelling of the knee.

There is a difference of opinion concerning whether to remove simply the torn portion of the cartilage or the entire meniscus. In repair of bucket handle tears, the torn portion is removed, and the border of the remaining portion is cleanly excised without removal of the entire cartilage. For other types of tears, most of the meniscus is removed, but a small rim is left. One should define the term when total removal is advised and indicate just what is done. The drawing shows



Anatomic relations of structures within the knee joint.

relations of structures within the knee joint. Anatomically, each meniscus, medial and lateral, is attached by its thick peripheral border to the deep aspect of the joint capsule. In addition, the peripheral borders of the cartilages are attached to the margins of the tibial condyles by short fibrous bands, known as coronary ligaments. The peripheral margin of the medial meniscus is firmly adherent to the broad and powerful tibial collateral ligament. Thus one should excise the meniscus at least flush with the capsule, leaving a rim, instead of attempting to separate it completely from its attachments.

In 2 cases torn cartilages in both knees were removed at one operation. The patients recovered as quickly and as perfectly as the average patient who has had only one knee operated on. No conclusions can be drawn from 2 cases, but because of them it may be assumed that the procedure is not contraindicated, and I shall not hesitate to repeat it for future patients.

The joints are irrigated with sterile isotonic solution of sodium chloride and closed in layers with fine interrupted silk sutures. In no case have sulfonamide drugs been used locally or by mouth, and no infections of any sort have occurred. In my opinion chemicals are not indicated for clean surgical wounds.

The postoperative care of patients with such injuries in former years was too prolonged. Granted that a primary principle of surgery is rest, yet it has been clearly shown that the quadriceps muscle, despite its bulk, atrophies quickly. When atrophy is extreme, it is almost impossible for the muscle to regain the pretraumatic status, and the knee joint is left relaxed and unstable. Recent reports emphasize the need for exercises of the muscles before and after surgical intervention, but, in addition, it is essential that the patient begin early weight bearing, except those with initial severe hemorrhage and significant reaction. In many cases of this series there was no form of immobilization used; but

TABLE 2.—Results of Treatment in One Hundred and Fifty-Five Cases of Torn Cartilage: All Types

	Age, Yr.	Splint, Days	Walk, Days	Degree of Flexion, Days	Squats on Heels, Days	Duty, Days
Averages.....	25.25	2.74	5.98	5.72	15.05	24.27
Extremes.....	15 to 42	0 to 5	2 to 11	3 to 15	7 to 25	9 to 60

The interval between injury and operation averaged 1.55 years.

for patients with noticeable swelling and sanguineous joint fluid a dressing of cotton wadding and Ace bandage was applied for two to five days. Table 2 demonstrates the time required for the return of function.

In the cases of early injury splinting was routinely carried out for five days, and weight bearing was permitted after seven days. It is not logical to use an identical procedure in all cases. In the average case in which operation was performed before other damage had been done, the knee joint was not injured by removal of the cartilage. The cartilaginous surfaces of the femur and tibia were intact and articulated as before, their contours being the same without necessity of adjustment of opposing surfaces, as in an arthroplasty. There is no contraindication to early walking except that of discomfort to the patient caused by the incision. This procedure was first put into practice with the patients with bucket handle tears, and the data of table 3 are given in support of the success obtained.

With the patient walking earlier, the return of function is facilitated. The period required

for return to regular duty is generally the same, because three weeks is considered soon enough for the patient to do all the physical exercises required during training. Three of the patients were in the Medical Department, not on field duty, and were allowed to return to work at their own request as early as nine and eleven days after the operations. They had full motion of the limb and no soreness, swelling or instability. As late as eight months after operation they still had no symptoms, and they are now on foreign duty. Early walking and exercise have

TABLE 3.—*Results of Treatment in Eighty Cases of Bucket Handle Tears*

	Age, Yr.	Splint, Days	Walk, Days	90 Degree Flex- ion, Days	Squat on Heels, Days	Duty, Days
Average of 80 cases...	25.60	2.59	5.53	5.52	16.92	21.66
Average for last 88 cases.....	25.23	1.58	3.54	6.42	14.36	21.02

since been done up to the patient's tolerance, and the results show a definite improvement. As a contrast to table 2, table 4 shows the averages for the last 50 cases of all types.

The only significant change in any factor in these 50 cases is less immobilization and earlier weight bearing in treatment; age, interval before operation and pathologic condition of the knee are essentially the same as in the whole group. These are consecutive cases, not selected any more than the entire series. The time of return to

TABLE 4.—*Results of Treatment in the Last Fifty Cases*

	Age, Yr.	Splint, Days	Walk, Days	90 Degree Flex- ion, Days	Squat on Heels, Days	Duty, Days
Average last 50 cases.	24.84	1.08	2.76	5.58	14.24	21.00

Interval between injury and operation averaged 1.74 years.

duty includes the additional days for those patients who returned to the hospital for further convalescence. It will be noted that for the entire series the extreme limit for return to duty was sixty days.

PROGNOSIS

Judging by the average results obtained with one method of treatment, can one with reasonable certainty estimate the final result before operation? This question is most important to the surgeon. The patient is not interested in averages but wants to know positively about his own case. The surgeon is generally pessimistic about the outcome in such cases, but this

pessimism is not justified in view of recent reports. An attempt is made here to determine what factors are of prognostic value. As far as this study can determine, age is no factor within the age limits of the patients that have been operated on, namely 18 to 42 years. The men over 30 were more stable and worked harder with the single purpose of rehabilitation, and all secured good stable knees and had no complaints.

The interval between injury and operation is of importance, depending on the occupation of the patient and in general on the number of recurrences of symptoms. In 155 cases these intervals were: nothing to six months, 72 cases; six to twelve months, 11 cases; one to two years, 10 cases; two to three years, 12 cases; three to four years, 12 cases; four to five years, 12 cases; five to six years, 8 cases; six to seven years, 11 cases; seven to eight years, 3 cases; nine years, 1 case; ten years, 2 cases, and 11 years, 1 case. An erosion of the cartilaginous surface of the femoral condyle directly overlying the torn

TABLE 5.—*Record of Follow-Up Observations*

Follow-Up:	6 Wk.	3 Mo.	6 Mo.	9 Mo.	12 Mo.	15 Mo.	25 Mo.	Total
By examination...	2	73	45	24	9	1	1	155
By letter.....	0	0	13	10	5	0	0	28
Final.....	1	46	58	34	14	1	1	155

portion of the meniscus is frequently seen in patients operated on several years after injury when there have been many recurrences of symptoms. This erosion is believed due to the pressure of the dislocated meniscus. The process is usually more extensive than is indicated in roentgenograms. When such changes appear, it is too late for the surgeon to accomplish a cure by meniscectomy. The mechanical impediment of blocked motion can be relieved, but a roughened articular surface and some pain remain. In a few cases erosion was seen as early as two years after injury, and it was not always shown in the roentgenogram. In the 3 cases in which the interval was from nine to eleven years, the surfaces of the joints were grossly normal and the results were good. Exact figures are not available for a large group of such patients examined in this camp but not operated on. So many patients with several recurrences of symptoms have shown moderate to extreme erosion of the femoral condyle and arthritic changes within four to five years after injury that the strong impression remains that conservative treatment for any one doing physical work

is a mistake. Surgical intervention is recommended within a short time after injury, when the acute phase has receded, and without delay in cases of the bucket handle tear that is not reduced by manipulation.

In addition to these 12 patients (7.74 per cent of the total number) there were 6 who had sore knees and were given light duty for a

TABLE 6.—Summary of Twelve Cases in Which Reclassification Was Necessary After Operation

Case No.	Age of Patient	Interval Between Injury and Operation	Pathologic Condition of Knee	Disposition
18	22	25 days	Lateral and transverse tear; normal joint	Discharge; atrophy of disuse; psychoneurosis
19	21	6 to 7 yr.	Transverse tear; severe erosion of femoral condyle	Discharge; damage to joint
31	22	3 to 4 yr.	Lateral tear; thick; normal joint	8 mo. full duty; discharge as psychoneurotic then
64	21	3 to 4 yr.	Bucket handle tear; normal joint	Reclassified; military police for 2½ yr.; pain reported; knee normal
89	27	6 to 7 yr.	Anterior and posterior tear; moderate arthritis	Reclassified; arthritis; still on duty, 15 mo.
84	22	3 to 4 yr.	Anterior and posterior tear; fat pad; normal joint	Discharge; atrophy of disuse; psychoneurosis
94	23	6 yr.	Posterior tear and hypertrophic fat pad	General duty for 1 yr.; then discharge for synovitis
126	18	2 yr.	Bucket handle tear; normal joint	Reclassified; quartermaster duty 10 mo.; no complaints
132	20	10 yr.	Bucket handle tear; was "locked" for 9 yr.	Light duty 8 mo.; discharge for unstable knee; painless
147	20	4 yr.	Posterior tear; joint normal	Reclassified; psychoneurosis
149	16	2 days	Bucket handle tear; normal joint	Full duty 3 mo.; no complaints; then acute gonococcic arthritis and discharge later
152	20	14 days	Posterior tear; normal joint	Discharge; atrophy of disuse; psychoneurosis, severe

few days at intervals over a two month period. When last examined, six months after the operation, they had no complaints or physical abnormalities. Five more had some soreness for three months but remained on full duty without loss of time; at six months they had no complaints and had normal knees. The remaining 132 (85.16 per cent) have had no complaints or physical abnormalities since they left the hospital and have been returned to duty as combat

soldiers. But 7 of these (4.51 per cent) had some changes in the joints at the time of operation, and it is expected that a longer follow-up observation will show some eventual disability, although they appeared normal at six months. With the exceptions noted, the patients in this series have gone back to their full duty directly from the hospital, not being placed on light duty for three to six months. It is a mistake to allow patients to remain long inactive, because those who have done so have had atrophy of the quadriceps muscle, with relaxed knees. There are 12 known failures, recorded in table 5, plus 7 expected disabilities, a total of 19 (12.25 per cent) of 155 cases. Without surgical intervention these men would have been definitely unfit for combat. What the results for these patients will be in five years or after the war, when other factors enter, are yet to be determined. In the meantime, these men have been rehabilitated and man power is conserved. Except for some evidences in cases 30, 80 and 132, there was nothing to indicate beforehand that in these cases results would not be good: age, interval since injury, history and examination are not infallible prognostic points. But if these criteria are favorable, the patient should not be denied the operation. The results of traumatic surgery are not all perfect.

VARIANT DIAGNOSTIC ENTITIES

Hypertrophic Infrapatellar Fat Pads.—This entity is in general only casually mentioned in discussion of derangements of the knee joint. It occurs more often than is realized, and the cause is unknown. The onset is usually gradual, not due to one acute injury. The patient states that the knee has ached or pained for various short intervals or suddenly "given way" while walking. The mechanism of strain and torsion, characteristic of cartilage tears, is generally absent. There is never "locking," although pain may be severe enough to cause guarded motion. Pain is often well localized anteriorly but can be referred with less intensity to the rest of the joint. In the cases of this type encountered in this series, swelling was diffuse, with noticeable increase of joint fluid. A well defined tongue of the hypertrophied pad, of variable consistency up to fairly dense fibrous tissue, is found at operation to extend into the joint space. One can easily see how such a tab can become squeezed between femoral and tibial condyles during extension of the knee, and erosion of the portion of the femoral condyle in contact with this tab is often seen. A mistaken diagnosis of torn meniscus may easily

be made before operation, depending on the history and on the severity of physical signs. Six derangements in this group were so diagnosed, but both the medial and the lateral menisci were found intact at operation. The hypertrophic fat tab is easily located, and it is necessary only to bear in mind the possibility of its being present, so that normal cartilages

TABLE 7.—*Return of Function After Correction of Hypertrophic Fat Pad*

	Age, Yr.	Splint, Days	Walk, Days	90 Degree Flex- ion, Days	Squat on Heels, Days	Duty, Days
Average of 15 cases...	35.40	2.40	6.66	10.06	23.73	31.04

are not removed and so that pathologic conditions may not remain. These cases definitely present more of a problem of convalescence than cases of torn cartilage. Despite a closure of the defect remaining in the infrapatellar fat pad after excision of the hypertrophied portion, there is more reaction of swelling, soreness and synovitis after operation. Functional return is slower, as is shown in table 7.

All the patients of this series who were operated on for correction of hypertrophic fat pads returned to full combat duty, without complaints, except 3, who were reclassified (table 8).

TABLE 8.—*Unsatisfactory Results After Correction of Hypertrophic Fat Pad*

Case No.	Age of Patient	Interval Between Onset and Operation	Pathologic Condition of Knee	Disposition
34	24	5 mo.	Hypertrophic fat pad; chronic synovitis	Reclassified; chronic synovitis
44	23	(1)2 days	Hypertrophic fat pad; joint mouse; osteochondritis of both knees	Reclassified; chronic synovitis
105	21	3 yr.	Hypertrophic fat pad; joint normal	Reclassified; pain; no physical abnormalities

The 3 men who were reclassified are now doing full duty in noncombatant units, including exercises and drill; but 3 reclassifications in 15 cases indicate that 20 per cent of the results were poor. From the surgeon's standpoint, however, there were good results in cases 34 and 105, because the patients after one year on duty have normal knees without physical abnormalities.

Osteochondroma.—Twenty patients with osteochondroma were operated on during that period in which men were inducted for limited service and were never intended for combat duty. The derangements were uniformly longstanding previous injuries with adequate histories and evidence, always verified by roentgenogram. The operations were done because

TABLE 9.—*Restoration of Function in Twenty Cases of Osteochondroma*

	Age, Yr.	Splint, Days	Walk, Days	90 Degree Flex- ion, Days	Squat on Heels, Days	Duty, Days
Average of 20 cases...	26.55	2.45	6.10	9.40	21.20	25.95

of acute exacerbations, and the patients were most grateful. They have had difficulties for several years, and the annoyance of frequent blocked motion and severe traumatic synovitis was relieved, although when damage to the joint is present one cannot give back a normal joint and cure the soreness caused by eroded joint surfaces. Results in these cases are shown in tables 8 and 9.

Five of 20 patients were given other duty or discharged, indicating 25 per cent poor results. However, these men were not able to do general

TABLE 10.—*Results of Operation for Osteochondroma Leading to Reclassification or Discharge*

Case No.	Age of Patient	Interval Between Injury and Operation	Pathologic Condition of Knee	Disposition
36	23	6 mo.	Joint mouse; osteochondritis dissecans	Reclassified; synovitis and soreness
38	24	2 1/4 yr.	Joint mouse; osteochondritis dissecans and arthritis	Discharged; arthritis
85	26	7 yr.	Joint mouse; osteochondritis dissecans	Reclassified; synovitis, mild
91	25	8 yr.	2 joint mice; osteochondritis dissecans	Reclassified; synovitis, mild
100	22	6 yr.	Joint mouse; normal knee	Full duty military police 1 yr.; discharge with recurrent mouse

duty on induction, and for those who were reclassified and still remaining on duty the operations cannot be termed failures. Thus there are but 10 per cent who have not been helped. Fifteen men of this group are now doing full combat duty and have thus been reclaimed from a limited status.

SUMMARY.

Operative results in consecutive series of 155 cases of torn semilunar cartilages were analyzed. This analysis showed that lack of immobilization, early exercises and weight bearing give quicker return of function. It indicated that simple excision of bucket handle tears is sufficient, and in so-called complete excision a thin margin of cartilage should remain. One hundred and thirty-two men (85.16 per cent) have returned directly to regular duty on an average of twenty-five days following operation for in-

juries incurred from a few days to eleven years before. The results justify immediate operation, because the total time lost from recurrence of injury will be considerably more with conservative treatment. Also the longer the torn cartilage remains the more likely it is that joint surfaces will become damaged and that a complete cure cannot be obtained. Hypertrophic fat pads are not generally recognized as a frequent derangement of the knee joint, but operation is warranted because of recurrences of symptoms and possible damage to the joint.

SOME RECENT ACCOMPLISHMENTS OF THORACIC SURGERY

W. E. ADAMS, M.D.

CHICAGO

I appreciate the honor of being invited to give the lecture in honor of Dr. Carl A. Hedblom. The subject I have chosen is quite appropriate, since Dr. Hedblom was one of the pioneers in the development of this field of surgery. He was endowed with a spirit of investigation and a determination to overcome obstacles in solving the problem at hand. Almost unlimited courage was formerly needed to face the tremendous risks involved in certain new operations which today have a low mortality and seem commonplace. Much is owed to these early pioneers, for without their continued effort the development of thoracic surgery would have been considerably delayed.

Dr. Hedblom made many contributions in this field of surgery and was an outstanding teacher and an inspiration to his associates. It is unfortunate that he could not see the accomplishments of more recent years.

In order better to appreciate much of the surgical therapy of diseases of the chest as it is seen today, I shall briefly review its status as presented fifty years ago. The first comprehensive work on thoracic surgery was published in 1896 by Stephen Paget,¹ one of the foremost men in this field at the time. Most of his book of 462 pages dealt with traumatic wounds of the chest, infections and tumors of the chest wall and empyema. Mediastinal tumors if cystic were drained; otherwise, no operation was advised. Cavities in the lung were apparently opened and drained externally, whether tuberculous or pyogenic. Less than ten pages of the entire book were devoted to intrathoracic malignant tumors, and these consisted chiefly of case reports. His prediction for the future could not have been farther from the truth when he stated: "It is sometimes said that surgeons fifty years hence will think as little of our results as we think of

the methods of fifty years ago. So far as regards the surgery of the chest this is utterly untrue. Fifty years ago it had risen above the horizon. It is now nearly at its zenith."

A careful survey of the factors involved which have delayed the development of thoracic surgery enables one to group them under three headings: (1) altered cardiorespiratory function due to disturbance of intrathoracic pressures, (2) methods of diagnosis and (3) resection of pulmonary tissue.

PHYSIOLOGIC CONSIDERATIONS

One of the major factors which retarded intrathoracic surgery was the fear of an open pneumothorax. The dangers associated with this condition were recognized by the ancient Greeks, but they understood little of the underlying principles on which they were based. As early as the sixteenth century, however, some knowledge of the influence of altered intrathoracic pressures on cardiorespiratory function was gained from animal experimentation.

The anatomist at Padua, Andreas Vesalius,² demonstrated the dangers of an open pneumothorax to his students. He exposed the transparent parietal pleura, through which the movements of the lung could be seen. When this membrane was broken, the lung would fall away from the side wall but the motion of the chest remained unchanged. If the other pleural cavity was opened, "the lungs are seen as the result of perforation to fall together and collapse. The cardiac motion may not be observed for long, since suffocation of the animal will come on account of the collapse of the lungs. In order to restore the life of the animal, an opening is made in the upper part of the trachea, into which a pipe made from a reed is introduced and when it is blown into, if the lung rises up, the animal receives air. The lung should be inflated to the degree to which it occupied the thorax in life. The heart now gathers strength and its motion

From the Department of Surgery of the University of Chicago.

Hedblom Lecture, presented on Jan. 24, 1945, at the University of Illinois College of Medicine.

1. Paget, S.: *The Surgery of the Chest*, Bristol, John Wright & Co., 1896, pp. 207 and 398-407.

2. Vesalius, A., cited by Homans, J.: *A Textbook of Surgery*, Springfield, Ill., Charles C Thomas, Publisher, 1931, p. 760.

will change beautifully. Therefore, by maintaining repeated inflation of the lung, you may have opportunity to examine the motion of the heart both by touch and sight as much as you desire."

Thus one sees that Vesalius understood both the untoward effects on the cardiorespiratory function of open pneumothorax, with its alterations of intrathoracic pressures, and a means of avoiding these harmful effects or of overcoming them once they were established. For centuries the dangers of an open pneumothorax were remembered, but the principle involved in the method of overcoming or obviating them was forgotten, or at least it was not associated with thoracic problems.

Methods, procedures and even principles seem to have a way of being reborn or discovered again and again, and so it was with the present principle involved. Von Mikulicz³ set Sauerbruch⁴ to work on the problem of intrathoracic surgery, and as a result the negative pressure room was constructed. Shortly thereafter, the positive pressure method of maintenance of expansion of the lung was elaborated on and perfected by Meltzer and Auer.⁵ The principle involved, that is, maintenance of inflation of the lungs, was the same with both types of pressure, one working from within the air passages and the other from without. The method of Meltzer and Auer, which made use of intratracheally induced anesthesia under positive pressure, had considerable advantage over that of the negative pressure chamber in that it was much less expensive, was much simpler of operation and therefore lent itself for a wider usage. In spite of Meltzer's work and Elsberg's application of the results to clinical surgery, a state of confusion continued to exist regarding the ill effects of an open pneumothorax. During the influenza epidemic of 1918 empyemas complicating the influenzal pneumonias were accompanied with an extremely high mortality when treated by early open drainage. The work of Graham and Bell, of the Empyema Commission of the United States Army, presented irrefutable evidence that the risk of an open pneumothorax was directly proportional to the size of the opening in the chest wall and indirectly proportional to the vital capacity.

That the collapse of the lung which occurs during an exploratory thoracotomy is not in itself

especially harmful and does not reduce the normal lung capacity to a lethal level has been repeatedly demonstrated. Both animals and human beings may well tolerate reduction in pulmonary function to a high degree; namely, one third to one sixth of their normal capacity.⁶ This fact is borne out by the frequent observation made during exploratory thoracotomy that the mobile mediastinum sinks well over the midline toward the side not operated on and thus impinges materially on the function of the presumably normal lung.

METHODS OF DIAGNOSIS

A second major factor causing delay in the development of thoracic surgery was the lack of diagnostic methods. With the discovery of the roentgen rays by Roentgen⁷ in 1895 and the subsequent finding of an opaque medium, the possibility of diagnosis of many lesions was much enhanced. The first successful use of the bronchoscope for removing foreign bodies from the air passages was accomplished by Killian⁸ in 1897. This was another great step forward, not only in the establishment of a correct diagnosis during an earlier stage of the disease but also in the realization of its frequent occurrence. Through its use a differentiation between pulmonary infection and pulmonary neoplasm is possible in a high percentage of cases. Patients with bronchiectasis may have a more complete diagnosis and their course of treatment may be more intelligently planned.

RESECTION OF PULMONARY TISSUE

The slow development of a suitable technic for lobectomy and pneumonectomy in human beings was not due to a lack of interest in this subject. The first total pneumonectomy was performed experimentally by Rolandus⁹ in 1492. In 1881 Gluck¹⁰ removed the entire lung on one side from 6 dogs and 8 rabbits, of which 2 of the latter survived. Friedrich¹¹ in 1908, by use of

6. (a) Rasmussen, R. A.; Adams, W. E., and Hrdina, L. S.: Should the Pleural Space Be Reduced in Size in the Resection of Lung Tissues? *Surgery* 10:85, 1941. (b) Graham, E. A.: With How Little Lung Tissue Is Life Compatible? *ibid.* 8:239, 1940.

7. Roentgen, W. C.: Concerning a New Kind of Ray, *Am. J. Roentgenol.* 10:320, 1923.

8. Killian, H., cited by Clerf, L. H.: Foreign Bodies in the Air Passages, *Ann. M. Hist.* 8:547, 1936.

9. Rolandus, cited by Murphy, J. B.: *Surgery of the Lung*, J. A. M. A. 31:341 (Aug. 13) 1898.

10. Gluck, T.: Experimenteller Beitrag zur Frage der Lungenextirpation, *Berl. klin. Wchnschr.* 18:645, 1881.

11. Friedrich, P. L.: Ueber den Raumaussgleich in der Brusthöhle nach einseitiger Lungenamputation, nebst Bemerkungen über das operative Mediastinalempysem, *Verhandl. d. deutsch. Gesellsch. f. Chir.* 37:571, 1908.

3. von Mikulicz, cited by Killian, H.: Scope and Utility of Differential Pressure in Thoracic Surgery, *Anesth. & Analg.* 17:154, 1938.

4. Sauerbruch, E. F.: Present Status of Surgery of the Thorax, *J. A. M. A.* 51:808 (Sept. 5) 1908.

5. Meltzer, S. J., and Auer, J.: Continuous Respiration Without Respiratory Movements, *J. Exper. Med.* 11:622, 1909.

the principle of dissection and separate ligation of vessels, was able to secure a favorable mortality rate in animals. Subsequently, with improvements in surgical technic, pneumonectomy in dogs has been carried out with less than 10 per cent mortality.

Lobectomy for tumor and for bronchiectasis was accomplished as early at 1907 by Gluck, whose results were later improved by Sauerbruch. Although the first pneumonectomy on an animal was performed as early as 1492, the first successful pneumonectomy for tumor in a human being was not made until 1933, almost four and one-half centuries later, by Graham.¹² This delay has been explained in part as owing to the lack of inherent healing in the bronchial wall by Bettman,¹³ whose experiments were substantiated by others.¹⁴ It was partly for this reason that mass ligation of the hilar structures was discarded in favor of the dissection technic. This consisted in individual ligation of the vessels and suturing of the bronchus followed by covering of the same with mediastinal pleura to encourage primary healing of the bronchial stump. More recently, compensatory changes following the reduction in pulmonary function and the amount of lung tissue which may be safely removed have been studied experimentally.¹⁵ By a combination of resection and collapse of the lung produced by bronchial stenosis, a dog's total lung capacity may be reduced to one upper lobe.^{6a} This represents a decrease of approximately 85 per cent of the entire lung volume. The remaining aerated lobe becomes overinflated and herniates to the opposite side. The animal when at rest is normal to all outward appearances but is somewhat dyspneic on exercise. Hematologic studies reveal a definite increase of blood flow through the inflated lung within a few hours after the resection.

When dogs with decreased pulmonary function and normal dogs are subjected to rarefied atmospheres, a high degree of pulmonary reserve is demonstrated. For example, when normal dogs were placed in a pressure chamber, they were able to tolerate a reduction in pressure to approximately 221.6 mm. of mercury, or an altitude of 30,400 feet (9,120 meters), a pressure similar to that withstood by human beings before becoming unconscious. Similar results were obtained when dogs with three pulmonary lobes functioning (upper lobe of both lungs and the middle lobe of the right lung, or about 38 per cent of normal) were subjected to the test. When dogs with one lobe functioning were tested they became unconscious at a pressure of 272 mm. of mercury, or an altitude of 25,833 feet (7,750 meters), thus showing a high reserve in spite of the fact that only a small per cent of the pulmonary tissue was functioning. These dogs have been observed for a period of over four years and appear to have compensation at the end of that time as good as or better than immediately or a few weeks after recovery.^{6a}

The ability of the dog to withstand decided reduction in pulmonary function has an important clinical application in the treatment of pulmonary infections and tumors by resection and collapse of the lung.

One of the most outstanding achievements of thoracic surgery has been the development of the surgical treatment of pulmonary tuberculosis. Collapse therapy in the form of pneumothorax, first suggested by James Carson, of Liverpool, in 1821, was first practiced by Forlanini, of Pavia, in 1882. The value of this form of treatment was soon appreciated. However, owing to the presence of pleural adhesions, the procedure lent itself to the treatment of only a limited number of patients. Thus the operation thoracoplasty was devised and was first attempted by Cernville, of Lausanne, in 1885. This procedure at first consisted in the removal of ribs over the area of pulmonary involvement. Brauer modified the operation so that a high degree of collapse was obtained at one operation. This was found to be too dangerous, however, the mortality being about 50 per cent. It was therefore modified again, by Friedrich and Wilms and later by Sauerbruch, but to Brauer and Friedrich is due much of the credit for the development of the operation as it is performed today. In 1925 Alexander¹⁶ made a complete survey of the literature, in order to evaluate the results of thoracoplasty in the treatment of tuberculosis.

16. Alexander, J.: *The Surgery of Pulmonary Tuberculosis*, Philadelphia, Lea & Febiger, 1925.

12. Graham, E. A., and Singer, J. J.: Successful Removal of an Entire Lung for Carcinoma of Bronchus, *J. A. M. A.* 101:1371 (Oct. 28) 1933.

13. Bettman, R. B.: Experimental Closure of Large Bronchi: A Study of the Factors Concerned in Failure of the Bronchi to Heal, *Arch. Surg.* 8:418 (Jan., pt. 2) 1924.

14. Adams, W. E., and Livingstone, H. M.: Bronchial Injury and Repair: An Experimental Study, *Ann. Surg.* 91:342, 1930.

15. Drastich, L.; Adams, W. E.; Hastings, A. B., and Compere, C. L.: The Effect of Exercise on the Acid-Base Balance and Oxygen of the Blood Following Atelectasis and Pneumectomy, *J. Thoracic Surg.* 3:341, 1934. Carter, B. N.; Longacre, J. J., and Quill, L. M.: A Study of the Changes in Cardiorespiratory Physiology Following Total Pneumectomy in Young Developing Animals, *ibid.* 7:329, 1938. Heuer, G. J., and Dunn, G. R.: Experimental Pneumectomy, *Bull. Johns Hopkins Hosp.* 31:31, 1920.

He found that 66.66 per cent of the 1,159 patients reported on were either cured or improved, whereas the remainder were unimproved or made worse. The recognition of the dangers associated with too rapid collapse of the diseased lung at one operation led to its being performed in stages. More recently, attention has been focused on the preoperative and postoperative care of the patient and the collapsing of only that part of the lung involved, thus sacrificing as little good lung as possible. In this way it has been possible to collapse cavities in both apexes by the resection of long segments of the upper three to six ribs over these lesions. In recent years a survey has shown that collapse therapy for pulmonary tuberculosis is commonly employed for from 80 to 90 per cent of the patients in large sanatoriums. For as high as 90 per cent of those patients receiving thoracoplasty the disease has been reported as arrested or greatly improved. With improvements in preparation of the patient and reduction in the amount of collapse at one stage, the operative mortality has been reduced to as low as 1 or 2 per cent. Allied operations, such as interruption of the phrenic nerve, paraffin plombage compression and the severing of adhesions to convert an inadequate pneumothorax into a satisfactory one, have been frequently used in selected cases. More recently, other methods of treatment include extrapleural pneumothorax, drainage of cavities and resection of lung tissue. It is too early to know at the present time how useful these methods may prove to be. The goal strived for is selective collapse therapy with conservation of all possible functioning lung tissue. Different methods of collapse therapy may be used simultaneously on one or both sides of the chest. In order to obtain the best possible results, cases must be individualized and therapeutic measures administered accordingly.

Probably the first operation on the thorax to be more or less generally accepted was the open drainage of acute empyemas. However, the high mortality associated with this operation led, until after the time of Lister, to the common practice of repeated aspiration. The frequent occurrence of a chronic empyema with such treatment stimulated the development of radical procedures, such as that devised by Estlander in 1879, by Schode in 1890 and, later, independently by Fowler and DeLorme in 1893. The results of these operations were far from satisfactory, and it remained for Baulu, in Germany, in 1896, to devise a method for open drainage of an empyema which obviated the dangers accompanying that operation. The principle involved was one of continuous siphonage of an empyema cavity.

The experimental work of Graham and Bell¹⁷ and others during World War I, concerning the physiology of the chest, demonstrated the dangers of open drainage if the mediastinum was not stabilized. It was shown that in cases of empyema complicating a streptococcic infection of the lung aspiration should be performed in the early phase, while the mediastinum is becoming fixed, whereas in cases of an empyema complicating a pneumococcic pneumonia the mediastinum becomes fixed relatively early and the danger of open drainage is thus obviated. In general, two principles resulted from their investigations: 1. Empyema is a surgical disease and should be treated by drainage. 2. Open operation is dangerous during the active stage of the primary disease and should not be made during this period. (The problem of empyema has recently been considerably reduced by the use of chemotherapy for pneumonia.)

The high mortality associated with collapse operations for chronic empyema led to further investigation of this problem. It is to Dr. Hedblom that much credit is due for the development of what he termed "graded thoracoplasty." By dividing the operation into several stages, the amount of shock and loss of blood were considerably reduced and the operative mortality decidedly lowered.

The history of the surgical treatment of pulmonary abscess is difficult to trace but undoubtedly it dates back to the time of Hippocrates. Until modern diagnostic methods, including the roentgen rays (1895) and the bronchoscope (1898), became available, the efficacy of surgical treatment was regarded as too slight when compared to the great danger attending the procedure. The use of local anesthesia and the performance of the operation in stages, along with the knowledge of the danger of operating through an open pleural space, have greatly reduced the mortality of this operation. The advisability of operating before the lesion becomes chronic has been recognized during the past decade. In spite of advancements, the mortality rate attending the operative treatment of chronic pulmonary abscess has remained high (15 to 30 per cent). On the other hand, when the operation can be performed within the first three to six weeks the risk may be reduced to less than 5 per cent. Acute pulmonary abscesses are opened widely and maintained open with a gauze pack until healing is completed. This allows not only for free drainage but for aeration as well. Aeration is important for abscesses due to anaerobic infection.

17. Graham, E. A., and Bell, R. D.: Open Pneumothorax, *Am. J. M. Sc.* 156:839, 1918.

Chronic pulmonary abscesses also require adequate drainage and aeration, which usually call for several operative stages. Many months usually expire before complete healing is effected. Residual bronchial fistulas and sinuses may be closed later by plastic operations. More recently, with the development of safer methods for resection of lung tissue, removal of the diseased area by lobectomy or pneumonectomy is the procedure of choice in selected cases.

In 1873 Mosler proposed incision and drainage of a bronchiectatic cavity. Much attention was given to the treatment of this condition by Leshartz, Quincke, Tuffier, Brauer and others. It was soon found that pneumotomy did not adequately drain the many bronchial dilatations, and therefore compression therapy began to be used. Hedblom,¹⁸ in 1931, reported on a series of patients treated by thoracoplasty. At first he was enthusiastic about this form of compression therapy, but he soon realized that it left much to be desired. Thus the operation lobectomy, which had been first performed by Heidenhain¹⁹ in 1901, was revived.²⁰ However, the mortality of the operation remained high, Graham finding it to be 52 per cent in 48 reported cases. For this reason, in 1925²¹ he devised an operation termed "cautery pneumonectomy" and reported 20 cases with an operative mortality of 20 per cent. Interest in lobectomy was again revived, by Brunn²² in 1929 and by Shenstone and Janes,²³ the former reporting 6 operations, with success in 4, no improvement in 1 and death in 1. Since that time a gradual improvement in the technic of the operation, with emphasis placed on preoperative and postoperative care, led to a striking reduction in mortality, the rate reaching as low as 5 per cent or less within the past few years.²⁴

Several authors have reported a series of 25 or more lobectomies for bronchiectasis without a

18. Hedblom, C. A.: Graded Thoracoplasty for Unilateral Bronchiectasis, *Wisconsin M. J.* 21:48, 1922.

19. Heidenhain, L.: Ausgedehnte Lungenresection wegen Zahlreicher eiternder Bronchiectasien in einem Unterlappen, *Verhandl. d. deutsch. Gesellsch. f. Chir.* 30:636, 1901.

20. Lilienthal, H.: *Thoracic Surgery*, Philadelphia, W. B. Saunders Company, 1925, vol. 2, p. 216.

21. Graham, E. A.: Pneumectomy with Cautery, *J. A. M. A.* 81:1010 (Sept. 22) 1923; Cautery Pneumectomy for Chronic Suppuration of Lung, *Arch. Surg.* 10:392 (Jan., pt. 2) 1925.

22. Brunn, H.: Surgical Principles Underlying One-Stage Lobectomy, *Arch. Surg.* 18:490 (Jan., pt. 2) 1929.

23. Shenstone, N. S., and Janes, R. M.: Experiences in Pulmonary Lobectomy, *Canad. M. A. J.* 27:138, 1932.

24. Blades, B., and Dugan, D. J.: Modern Pulmonary Resection in War Surgery, *S. Clin. North America* 23:1545, 1943.

single death.²⁵ This represents truly a phenomenal advance in the treatment of this condition. Persons with bilateral bronchiectasis are now accepted for treatment more frequently than formerly. Some patients may have four of their five pulmonary lobes involved and still be amenable to treatment. In such cases the resection must be made in two or three stages, with an interval of several months between. In view of the large respiratory reserve which is present in normal persons, patients are able to tolerate bilateral resections of one half to two thirds of the lung and have sufficient capacity remaining to enable them to enjoy reduced exercise and a reasonably normal life. In a recent review of 45 operations made on 36 patients at the University of Chicago hospitals there were 2 deaths due to the operation, both following the first stage in cases of bilateral involvement. Twenty-nine of the 45 operations were made on 20 patients with bilateral disease. The treatment for some of these patients has not been completed. At the present time 7 patients have had bilateral resections, with good results. When the dissection technic type of operation and chemotherapy are employed, postoperative complications are much less frequent; accordingly, the morbidity has been significantly reduced (3 empyemas and no bronchial fistulas in 22 patients).

The next condition to consider is primary carcinoma of the lung. In Paget's time this was thought to be a rare disease. However, recent statistics reveal that it comprises approximately 8 per cent of all malignant tumors; thus the magnitude of its importance is obvious.

Attempts to cure this tumor by irradiation have been extensively made for years but with little success. In 1933 Graham¹² successfully performed a total pneumonectomy and a partial thoracoplasty in one stage for bronchogenic carcinoma of the left lung. The patient was a 48 year old physician, and at the present time, twelve years later, he is carrying on an active practice. This successful case stimulated much interest, and to Graham, Rienhoff, Churchill, Overholdt, Alexander and many others is due credit for the development of the surgical principles now recognized in its treatment.

The successful surgical treatment of bronchogenic carcinoma, as is true of other malignant tumors, depends largely on early diagnosis. Because of the variable clinical course, with cough,

25. (a) Churchill, E. D.: Resection of the Lung, *Surgery* 8:951, 1940. (b) Maier, H. C.: The Surgical Treatment of Bronchiectasis, *ibid.* 15:789, 1944. (c) DeBakey, M., and Ochsner, A.: Surgical Treatment of Bronchiectasis, *Dis. of Chest* 9:63, 1943.

hemoptysis, fever, pain in the chest, loss of weight and strength and the like, the lesion is frequently diagnosed as pneumonia, tuberculosis or pulmonary abscess, and valuable time is lost while the patient is treated for one of these conditions.

The clinical symptoms and physical observations are extremely variable, not only in different patients but at different periods in the same patient. In general, one can say that a large proportion of the symptoms are on the basis of infection of the respiratory passages due to varying degrees of obstruction by the tumor. To a lesser extent symptoms are produced by direct invasion of adjacent structures. On the other hand, many tumors located in the peripheral portion of the lung remain quiescent for months or even years, regardless of the type of tumor cells or their arrangement.²⁶ Again, as previously mentioned, central necrosis with cavity formations and infection in some tumors produces symptoms and signs of pulmonary suppuration, tuberculous or nontuberculous in nature.²⁷ It will be apparent at once that the sooner symptoms are produced by a tumor, the greater the likelihood that an early diagnosis will be made, provided diagnostic methods are properly used. Thus, tumors which remain "silent" and are found only late in the course of the disease will have a much poorer prognosis, provided their degree of malignancy is the same.

One of the principal factors in diagnosis is suspicion of the presence of tumor in all patients over 40 years of age having symptoms referable to the chest. When the high incidence of the tumor is kept in mind, a search will be rewarded by a higher percentage of early diagnosis. If fluoroscopic examinations were made as a routine at regular intervals on all patients in this group, a higher percentage of the peripheral lung tumors would be diagnosed at an earlier stage, thus improving the prognosis for this group. For the centrally located variety, bronchoscopic examination and biopsy of the tumor in all patients with unexplained cough would give rise to an early diagnosis, even before roentgenologic evidence is demonstrable.

Since bronchoscopic examination with biopsy of tumor tissue is applicable in 60 to 75 per cent of all cases of primary pulmonary carcinoma, it remains the most valuable procedure for improving surgical treatment.

In the differential diagnosis one of the most difficult conditions to be differentiated from

peripherally located carcinoma is pulmonary tuberculosis. As already pointed out by Hausner and Wolpaw,²⁷ cavitation occurs in about 12 per cent of the tumors, and both roentgenologically and clinically they may simulate the appearance of pulmonary tuberculosis. Again, one may occasionally see a solitary tuberculous lesion which produces an opaque shadow on roentgen examination and which appears not unlike a peripherally located primary pulmonary tumor. (The rate of change in roentgenologic appearance is not always diagnostic.) In the later stages of the tumor, empyema and nontuberculous pulmonary abscesses are often presented as the primary diagnosis. Again, in cases of the benign, centrally located tumors, bronchitis and repeated attacks of pneumonia due to the presence of infection of the air passages are commonly mistaken as the primary diagnosis. It is evident that when these lesions are found in patients in whom primary carcinoma is likely to be found an early differentiation can be made only by observation and by the use of available diagnostic methods.

TREATMENT

Until within recent years, surgical extirpation of lung tissue for carcinoma was attended by great a risk that most pulmonary tumors were treated either by bronchoscopic removal or high voltage roentgen therapy. After years of investigation, hundreds of patients being treated by this method, it has become generally believed and more recently quite definitely proved that bronchogenic carcinoma has not been cured by roentgen therapy.²⁸ In a recent communication Steiner²⁹ has reported the results of roentgenologic treatment and its histologic effects on both the primary growth and the metastatic lesion. In no patient was a cure effected, and survival was not noticeably prolonged by the irradiation.

Surgical treatment has been carried out sporadically for several decades. In 1911 a monograph on the subject was published by Adler,³⁰ who stated: "There is every reason to hope that the technique of this new branch of surgery will be still further developed and that the near future thoracotomy and operations"

26. Thornton, T. F., Jr.; Adams, W. E., and Bloch, R. G.: Solitary Circumscribed Tumors of the Lung, *Surg., Gynec. & Obst.* 78:364, 1944.

27. Hauser, H., and Wolpaw, S. E.: Cavitary Bronchogenic Carcinoma, *Radiology* 34:698, 1940.

28. Bloch, R. G., and Bogardus, G.: *Bronchogenic Carcinoma, with Special Reference to Results of Roentgen Therapy*, *Arch. Int. Med.* 66:39 (July) 1912. Graham and Singer.¹²

29. Steiner, P. E.: Effects of Roentgen Therapy on Histologic Picture and on Survival in Cases of Primary Carcinoma of Lung, *Arch. Int. Med.* 66:1 (July) 1940.

30. Adler, I.: *Primary Malignant Growths of the Lungs and Bronchi*, London, Longmans, Green & Co. 1912.

will be attended by no more risk than 1 operations today. If this is so, a new at responsibility is placed upon the s of internal medicine. It will be neces- only to educate the opinion of the laity nduce them to submit to these operations : same readiness with which they now o peritoneal operations, but it will also be ed duty of the physician to recognize uses and to recognize them as early as . When all the means of diagnosis out- this little study fail, where there is sus- of tumor, but no assurance is possible, ould be—it is emphatically here stated— hesitation in resorting to an exploratory tomy as there is now in submitting to an tory laparotomy." Adler's prediction has tance come true, and when his suggestions lowed beneficial results from surgery can ected.

ration.—The anesthesia for pneumonec- as well as for all intrathoracic operations facilitate good exposure, provide adequate nation and support respiration and circu-

It should necessitate minimal motion of ngs and the least interference with cardio- atory function and minimize postoperative ications. Ethylene plus oxygen plus ether istered through a snug-fitting face mask a positive pressure technic has been found a satisfactory anesthetic for these operations. e earlier operation performed for primary onary tumors consisted chiefly in the rel- of one lobe or a portion of a lobe of a lung. equent observations revealed that in a high- ntage of patients for whom this procedure carried out recurrence of the tumor or con- ition of growth of the metastases was apt to lt. The operation of choice, therefore, was d to be a total pneumonectomy with resec- of the mediastinal lymph nodes. In perfor- ce of a total pneumonectomy, careful dissec- of the vessels and bronchus at the hilus with vidual ligation of the former is the procedure hoice. This enables a higher division of the nary bronchus and an adequate exposure for oval of mediastinal lymph nodes. Thus, by ection of an adequate amount of the tumor- ring tissue at its primary site and of the onal lymph nodes which are the first to be olved by metastases, a much higher percentage permanent cures may be expected.

That there remains an indication for lobectomy the treatment of a group of slow-growing onchial tumors is a view held by most authors. his group of tumors originates in the primary em bronchi, and they are slow to invade

adjacent structures or to metastasize. Since the risk of pneumonectomy still remains appreciably higher than that of lobectomy, if the latter operation is adequate to remove all tumor-bearing tissue it is thought to be the procedure of choice for this group of patients.³¹

Results of Surgical Treatment During the Past Decade.—An appraisal of the accomplishments of any surgical procedure by the use of statistical material is usually far from satisfactory. However, some information can be gained from reports of personal experience or collected cases which have appeared in the literature.

In 1941, at the twenty-fourth annual meeting of the American Association for Thoracic Surgery,³² pneumonectomy for bronchogenic carcinoma of the lung was thoroughly discussed and the following statistics were given: E. F. Butler, 16 operations with 4 deaths; S. W. Harrington, 9 operations with 3 deaths; R. H. Overhold, 28 operations with 8 deaths; W. F. Rienhoff Jr., 46 operations with 10 deaths, and N. S. Shenstone, 13 operations with 6 deaths.

More recently Rienhoff³³ reported a series of 71 pneumonectomies with 15 deaths, or a mortality of 21 per cent, and Graham³⁴ had performed 77 operations during the past five years with 23 deaths, or a mortality of 27 per cent. In Graham's last 33 cases there were only 5 deaths, or a mortality of 14.8 per cent. An even lower mortality rate was obtained by Ochsner who lost only 2 of his last 30 patients, or 6.66 per cent. At the University of Chicago Hospitals the over-all mortality has been 28 per cent. In the last 17 cases there have been 3 deaths, or a mortality of 17.6 per cent. Thus it is obvious that decided progress has been made during the short period of twelve years that successful surgical therapy has been employed.

The last condition which I wish to discuss in any detail is carcinoma of the esophagus. This has been the most recent intrathoracic malignant neoplasm to yield to radical surgical treatment.

Torek's³⁵ successful resection of the thoracic esophagus in 1913 gave rise to considerable in-

31. Adams, W. E.; Steiner, P. E., and Bloch, R. G.: *Malignant Adenoma of the Lung*, Surgery **11**:503, 1942.

32. Harrington, S. W.: *Pneumonectomy for Carcinoma of the Lung*, J. Thoracic Surg. **11**:396, 1942. Shenstone, N. S.: *Experiences with Total Pneumonectomy*, J. Thoracic Surg. **11**:396, 1942.

33. Rienhoff, W. F., Jr.: *The Present Status of the Surgical Treatment of Primary Carcinoma of the Lung*, J. A. M. A. **126**:1123 (Dec. 30) 1944.

34. Graham, E. A.: *Indications for Total Pneumonectomy*, Dis. of Chest **10**:87, 1944.

35. Torek, F.: *The First Successful Case of Resection of the Thoracic Esophagus*, Surg., Gynec. & Obst. **16**:614, 1913.

terest and hope in the management of this lesion. His operation consisted of dividing the esophagus below the site of the tumor, inverting the lower end and bringing the upper end with the tumor out at the base of the neck. The cervical portion of the esophagus was then connected to the stomach by means of a rubber tube. In spite of an abundance of investigative work and many attempts by a large number of surgeons to repeat Torek's accomplishment, only 14 successful resections were reported up to 1934,³⁶ and all the patients except Torek's died of metastases within two years following the operation.

This almost uniform failure to respond to therapeutic measures has been due chiefly to two factors: (1) lack of early correct diagnosis and (2) late development of principles of intrathoracic surgery.

The onset of the lesion is insidious, the condition frequently being advanced before symptoms become manifest. These symptoms are usually very mild when first noted, and little attention is given them by either the patient or the physician. They may be brought about by (1) mechanical obstruction of the passageway by the tumor or (2) by the influence of the tumor on adjacent structures.³⁷

Although not typical for this condition, dysphagia is the first and most outstanding symptom in the majority of cases. The location of the tumor signifies little in this respect except in the interval between the act of swallowing and the experiencing of a sense of obstruction. By far the majority of the tumors are located in the middle and lower segments of the esophagus, only approximately 10 per cent occurring in the upper portion.

The recent revival of interest in the surgical treatment of esophageal carcinoma is both timely and deserving. Its importance is more fully appreciated in view of the fact that it is fourth in frequency of all malignant tumors occurring in men over 20 years of age. In a survey compiling 124,827 autopsies from forty-two German pathologic institutions between 1925 and 1933, Dormanns³⁸ noted that it was surpassed in frequency only by cancer of the stomach, lung and rectum. Of 23,139 deaths due to malignant growths in

patients over 20 years of age, 8 per cent were due to this tumor.

A major part of the recent success obtained in surgical treatment of this tumor has been due to animal experimentation carried out in conjunction with clinical experience. Aided by establishment of surgical principles especially applicable to this field and by the improvements of surgical methods, resection of the esophagus in animals was attended with a high degree of success. From the results of experiments made in the laboratory, two principles of particular importance in this problem were established: 1. Anastomosis of the stomach and esophagus following the resection of a tumor should be made with two rows of interrupted sutures. By use of this technic, stenosis of the lumen at the site of anastomosis following operation seldom occurs. 2. Tension on the suture line due to insufficient elevation of the stomach for the anastomosis should be prevented, since it is apt to result in breakdown of the anastomosis, with leakage and subsequent mediastinitis. Further to prevent tension on the suture line, the stomach is held up in the chest by suturing it to the pleura, as suggested by Carter.

When clinical application of these principles was made the results were similar to those obtained on dogs.³⁹ Thus in January 1938, just seven years ago, a transthoracoabdominal resection of the lower part of the esophagus and esophagogastrostomy for a carcinoma of the lower part of the esophagus was made on a 53 year old woman by Dr. Phemister. Anesthesia was induced with ethylene and oxygen administered through a snug-fitting face mask under moderate positive pressure by Dr. Geraldine Light. This patient is living and without symptoms or evidence of persistence of the malignant neoplasm at the present time. This successful operation again stimulated interest in the surgical treatment of this tumor, and it was soon found that carcinoma

36. Adams, W. E.: Recent Progress in the Surgical Treatment of Carcinoma of the Esophagus, *Surg., Gynec. & Obst.* 72:312, 1941.

37. Adams, W. E.: The Pathological Consideration Relating to the Early Diagnosis and Curative Surgical Treatment of Carcinoma of the Esophagus, *Surg., Gynec. & Obst.* 72:105, 1941.

38. Dormanns, E.: Das Oesophagus Carcinom, *Ztschr. f. Krebsforsch.* 49:86, 1939.

39. Miller, R. T., Jr., and Andrus, W. DeW.: Experimental Surgery of Thoracic Esophagus, *Bull. John Hopkins Hosp.* 34:109, 1923. Heuer, G. J.; Andrus, W. DeW., and Bell, H. G.: The Experimental Transplantation of the Diaphragm as an Adjunct in the Treatment of Lesions at the Lower End of the Esophagus, *Ann. Surg.* 81:273, 1925. Saint, J. H., and Mann, F. C.: Experimental Surgery of the Esophagus, *Arch. Surg.* 18:2324 (June) 1929. Ohsawa, T.: The Surgery of the Esophagus, *Kyoto Imperial University*, 1934. Adams, W. E.; Escudero, L.; Aronsohn, H. G. and Shaw, M. M.: Resection of the Thoracic Esophagus, *J. Thoracic Surg.* 7:605, 1938. Carter, N. B., Stevenson, J., and Abbott, O. A.: Esophagogastrostomy, *ibid.* 10:446, 1941.

40. Adams, W. E., and Phemister, D. B.: Carcinoma of the Lower Thoracic Esophagus, *J. Thoracic Surg.* 7:621, 1938.

nomas of the stomach limited to the cardia and involving the esophagus secondarily were also more easily managed by an approach through the lower portion of the thorax.

In 1941 a survey revealed that 34 successful resections of the esophagus had been accomplished by twelve surgeons, with a mortality of 50 per cent.³⁶ This high mortality rate was partly due to the acceptance of patients for operation whose tumor had reached an advanced stage. In 1943 Churchill and Sweet⁴¹ reported 11 cases of resection of tumors located in either the lower part of the esophagus or the cardiac end of the stomach, with only 1 death. Garlock at about the same time had completed 22 resections, with 9 deaths.

It was soon noticed that tumors located in the lower third of the esophagus offered a much better prognosis than those of the middle third both as to operability and as to ultimate outcome. This is due to the fact that in a high percentage of cases of tumors located in the middle third invasion of the bronchus, trachea or aorta has already occurred before the patient reaches the surgeon. For those patients who have operable lesions (in the middle third) a recent improvement over the Torek operation has been a higher anastomosis between the esophagus and stomach, external to and above the arch of the aorta. This was first accomplished by Garlock in 1943⁴² and has subsequently been made in 3 patients at our hospital.

Up to the present time Dr. Phemister and I have made 33 resections, with 21 survivals. Of these, 27 were for tumors of the lower part of the esophagus or cardiac end of the stomach, with 17

recoveries; in my last 7 cases there has been 1 death.

Much of the success in the treatment of carcinoma of the esophagus and cardia has been due to the proper preparation of patients by the administration of fluids, electrolytes and blood and by the replacement of blood lost during the operation. Support of the circulation and adequate oxygenation by an anesthetic administered under moderate positive pressure has also been of primary importance. Chemotherapy may also be credited with the saving of some patients.

In spite of the progress made during the past decade, there remains much room for improvement. Education of the medical profession and the laity as to the frequency of this tumor and availability of surgical therapy when an early diagnosis is made will lead to a higher percentage of operable cases and surgical cures.

Recent advances in surgical treatment of the esophagus have not been restricted to malignant lesions. Relief of benign obstructions in the lower third by a side to side anastomosis between the stomach and esophagus above the site of obstruction is being reported in increasing numbers. This type of operation has been made in 6 patients at the University of Chicago Clinics with satisfactory results.

Time does not permit a detailed discussion of all the advances in this field of surgery in recent years. A number of conditions little known about in Paget's time have recently responded successfully to surgical management. Cystic disease of the lung and mediastinal tumors may now be managed without undue risk. Injuries of the heart, compressive heart disease and patent ductus arteriosus with or without blood stream infection are being successfully treated in a high percentage of cases. Thoracic surgery has truly made great progress, but with continued effort through scientific investigation and discovery, new horizons may be reached by the succeeding generations.

41. Churchill, E. D., and Sweet, R. H.: Trans-thoracic Resection of Tumors of the Stomach and Esophagus, *Ann. Surg.* **115**:897, 1942; **116**:566, 1942.

42. Garlock, J. H.: Reestablishment of Esophago-gastric Continuity Following Resection of Esophagus for Carcinoma of Middle Third, *Surg., Gynec. & Obst.* **78**:23, 1944.

MECKEL'S DIVERTICULUM CONTAINING CALCULI

ARTHUR W. ALLEN, M.D., AND GORDON A. DONALDSON, M.D.
BOSTON

It has been estimated by various authors that the incidence of Meckel's diverticulum lies between 1 and 2 per cent. Of these certainly few cause symptoms, and the pathologic changes as listed by Hudson¹ are certainly bizarre. Ochsner² and Miller and Wallace³ have correlated pathologic observations and symptomatology. In young persons, hemorrhage secondary to actual ulceration is most common, while in the adult group intestinal obstruction as a result of inflammation or torsion is found most frequent.

None of these sources mention stones within the diverticulum as a possible pathologic finding. A review of the literature⁴ reveals this complication to be rare, and the present report is the eleventh recorded case of their occurrence. In 7 of these 11 cases the lesion gave rise to symptoms. And as might be expected from the acute type and location of pain together with the physical and laboratory findings, in most instances the diagnosis of obstructive appendicitis was entertained. In 4 cases, including the 1 that we are reporting, the stones were found incidental to other abdominal pathologic changes. In no case in which roentgenologic examinations were made were the stones visible on the films. These stones are pigmented and have the appearance of gallstones, even to being faceted in some instances, and in earlier reports the belief was expressed that they were of gallbladder origin. Most evidence, including our own, however, is against this conclusion; and in the 1 case in

which chemical analysis was reported, by Hanke⁵ the composition of the stones was distinctly different from that found in biliary calculi. In most instances the stones consist of fecal matter with bile pigment. In the present case the diverticulum containing stones was found incidental to carcinoma of the cecum.

REPORT OF A CASE

The case to be reported is that of a 58 year surgeon. The past history was of special import in that he had had a cholecystectomy twelve years before present admission to the hospital. A gallbladder



View into the lumen of the diverticulum (from a 35 mm. Kodachrome negative). The bowel has been partially opened, allowing exposure of the conditions in the tip of the diverticulum.

containing four large stones had been removed. Thirteen years previously an appendectomy had been performed.

He had been followed over the previous six years by a consulting physician. During this time he had complained of easy fatigability and lack of endurance. At no time had he had abdominal pain. At the time of his admission to the hospital his chief complaint was that of great fatigue.

During the previous month he had frequently fainted while at work. Thirty-six hours before admission while operating, he was seized with a feeling of weakness, faintness and sweating. Several hours later passed blood clots and fresh bright blood in two loose bowel movements. There had been no cramps, and his bowels previously had been regular.

On admission he was found to have a red blood cell count of 3,730,000 and a hemoglobin content (phot

5. Hanke, H.: Presence of Biliary Calculi in Meckel's Diverticulum, *Centralbl. i. allg. Path. u. anat.* **57**:161, 1933.

1. Hudson, H. W.: Meckel's Diverticulum in Children, *New England J. Med.* **208**:525, 1933.

2. Ochsner, A.: Meckel's Diverticulum, in Nelson's Loose Leaf Living Surgery, New York, Thos. Nelson & Sons, 1928, vol. 5, p. 252.

3. Miller, R. H., and Wallace, R. H.: Meckel's Diverticulum in Acute Abdominal Emergencies, *Ann. Surg.* **98**:713, 1933.

4. Drummond, H.: Notes of Cases Illustrating Some of the Surgical Aspects of Persistent Meckel's Diverticulum, *Surg., Gynec. & Obst.* **16**:656, 1913. Mulsow, F. W.: Meckel's Diverticulum Containing Calculi, *Am. J. Digest. Dis.* **10**:188, 1943. Sherren, J.: Meckel's Diverticulum Containing Calculi and Producing Colic, *Proc. Roy. Soc. Med. (Clin. Sect.)* **3**:11, 1909-1910. Beach, H. H. A.: Case of Pelvic Tumor Formed by Calcified Meckel's Diverticulum Uniting Ileum and Bladder, *Ann. Surg.* **24**:484, 1896.

METHODS FOR REDUCING PAIN FOLLOWING HEMORRHOIDECTOMY

TECHNIC AND RESULTS IN SEVENTY-TWO CASES

JAMES C. OWINGS, M.D.

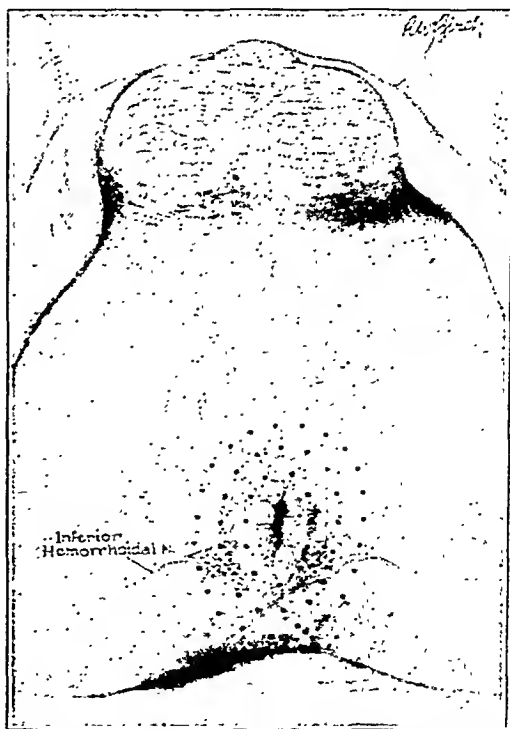
BALTIMORE

I have been interested in trying to lessen the pain associated with hemorrhoidectomy ever since it was my duty to remove the rectal plugs from patients during my internship. In 1930 I suggested to Dr. Harvey B. Stone, of Baltimore, that he use his method of local injection of alcohol into the perianal region for this purpose. He tried it on a few patients at that time but gave it up because of one or two sloughs followed by abscess formation. I also tried this method in a few cases at that time and have used it occasionally on very nervous patients during the past fourteen years. For the last three years I have used it routinely on my private patients and have been able to improve the technic greatly.

This report concerns the technic and results in 72 cases. Some of the patients had nothing but hemorrhoids, whereas the rest had either fissures or pruritus in association with hemorrhoids. No preoperative preparation has been given except for the usual enema and sedation with pentobarbital sodium. A combination of about 0.5 Gm. of dilute pentothal sodium followed by cyclopropane has been the anesthetic of choice because with it the patient is kept well oxygenated and seldom vomits, and there is, therefore, less likelihood of strain on the anal canal which might cause bleeding. The quick and pleasant induction and the absence of after-effects make this a very satisfactory anesthesia.

The field of operation is shaved and carefully scrubbed with 70 per cent alcohol, no attempt being made to sterilize the anal canal. Two coats of surgical solution of merbromin (alcohol, acetone and merbromin) are then applied and the field of operation is kept moist with this solution during the injection of the alcohol. A tuberculin syringe with a $\frac{1}{2}$ inch (1.3 cm.) hypodermic needle is used for the injection. It is essential to put only a drop or two of alcohol in at any one puncture site, and for this reason a tuberculin syringe is used because with a syringe of this caliber one can easily estimate

the amount, or actually measure it if one wishes. A $\frac{1}{2}$ inch needle is used because, while one must be sure to place the alcohol beneath the skin, one can control the depth better if the needle is short. If a long needle is used, one not only may fail to get the alcohol directly under the skin where one wishes it but may damage the nerve fibers entering the sphincter muscle by getting it in too deeply. Ninety-five per cent alcohol is



Dots represent puncture points for injection of alcohol when local anesthesia is desired and X's mark injection points when partial paralysis of the external sphincter is also indicated.

used, and the amount varies from 3 to 10 cc. or more, depending on the extent of associated pruritus. I have used as much as 30 cc. in 1 case in which the pruritus was extensive. However, the average hemorrhoid requires no more than 3 or 4 cc. for adequate anesthesia.

The injections are made in concentric circles which start at the anal margin, in an attempt to

block first the portion of the anal canal covered by stratified epithelium. The puncture wounds are made about 0.5 cm. apart, and the concentric circles, usually three, are about this same distance from one another. It is necessary to make sure that the flow of the alcohol from the syringe does not require any appreciable pressure, because if force is necessary it usually means that the point of the needle is embedded in the skin of the buttocks or anal canal; if injection is made in these circumstances, a slough is likely to occur. If the patient has a relaxed sphincter from long-standing prolapsing internal hemorrhoids, one has to be particularly careful about the depth of the punctures in order not to increase the relaxation by damaging the nerve supply to the sphincter. On the other hand, if the patient has a very spastic sphincter in association with a fissure and one wishes to produce relaxation, this can readily be done by making two or three injections to the full length of the needle at 5 and 7 o'clock, with the patient in the lithotomy position.

After the injections have been completed, the hemorrhoids are removed by dividing the mucosa longitudinally, ligating the vein and the artery at the highest feasible point and dissecting out the dilated venous plexus. Little mucosa is removed except in those instances in which there is a first degree prolapse of the mucosa in association with large internal hemorrhoids. In these cases, enough mucosa is removed to bring the anal canal back to normal size. A continuous locked suture of 00 plain surgical gut is used for closing the hemorrhoidal bed after all actively bleeding points have been ligated or transfixed. Great care is used not to catch the edges of the mucosa with this stitch but to place it in the same manner as one would a subcuticular stitch, that is, so that the mucosa is drawn together over it. This stitch is not carried clear to the skin margin, because I feel that approximation of the perianal skin edges, with subsequent infection and edema, has considerable bearing on the postoperative formation of skin tags. Any veins that remain between the linear incisions, either externally or internally, are crushed and partially evulsed by undermining the skin or mucous membrane with a Halsted clamp. If hematomas are produced during this procedure, they are evacuated and the bleeding points tied.

No rectal plug of any sort is used because not only is such a plug painful at the time of removal but, through reflex spasm of the sphincter, it interferes with voiding. It also prevents primary union of the mucosa by keeping the raw

areas open, thereby admitting gross infection during the immediate postoperative period. One leaves adequate mucosa, there is no danger of a stricture. It is hard to believe that the stretching of a circular muscle like the sphincter for a twenty-four hour period is likely to produce relaxation of this muscle for any appreciable period, this being one of the usual reasons given for the use of a rectal plug. Certainly there is no justification for using a plug to control hemorrhage, because if the bleeding is controlled at the time of operation it is no more likely to start up again in such a wound than it is in any other wound. In fact, it would seem that the removal of such a plug, plus the infection carried down to the fresh operative field by its contact with the gauze, is probably the source of many secondary hemorrhages rather than a preventive. It seems to me that the use of the rectal plug is more a relic from the past than a logical surgical procedure and for this reason should be given up. The only dressing used in this procedure is local gauze held in position by a perineal T binder.

Postoperatively these patients were given one ounce (30 cc.) of liquid petrolatum at night and morning; sitz baths were started the morning following the operation and were repeated twice daily and after bowel movements until healing was complete. No other cathartics were used but if the patient had not had a spontaneous movement by the third or fourth day an oil retention enema was given. Nothing more seriously disturbs the course of a patient who has had a hemorrhoidectomy than a strong cathartic. The patients were kept on a liquid diet for approximately five days in order to insure a minimum amount of intestinal residue. One wonders if it might not be better to give camphorated tincture of opium, rather than liquid petrolatum, together with low residue diet and possibly succinylsulfathiazole in order to allow primary healing to occur before the first movement takes place. Dilatation was carried out on the sixth or seventh day following operation by resting the finger gently against the anal margin and having the patient strain until the finger entered the anal canal. By the patient's straining, the sphincter relaxes, and the finger slides in without causing reflex spasm. The anal canal was again dilated at weekly intervals until healing was complete. I doubt if dilatation is necessary, provided the operation is done carefully enough to leave sufficient mucosa. Dr. Warfield M. Firor, of the Johns Hopkins University School of Medicine, has told me that he does not employ dilatation in his patients and that none of them has had a stricture.

There were no abscesses and no sloughs in any of this series of 72 cases, and I do not believe that enough of these complications will occur to be of any importance if the technic I have outlined is strictly adhered to, namely, working through a field which has been carefully prepared before the operation itself is started, making sure that the point of the needle is beneath the skin and depositing only 1 or 2 drops of the alcohol in one site. Relief of pain was somewhat variable. Some patients said that they could not tell that they had been operated on; others still had considerable pain. The degree of relief, however, has steadily increased as more experience has been gained with the method and at present certainly justifies the use of the procedure. Because of uncontrollable factors, I doubt whether a consistently perfect anesthesia can ever be obtained. Only 1 of my patients had to be catheterized after a twelve hour period of retention. There were no postoperative hemorrhages. One patient had to have removal of skin tags because of excoriation and itching. There were no instances of incontinence, but 2 patients did have some involuntary soiling for as long as three months.

Both of these had fissure in association with hemorrhoids, and a deliberate attempt was made to paralyze the sphincter. In these 2 patients the paralysis lasted longer than was desired. Both recovered completely. The majority of the patients have not been followed long enough to tell whether there will be any recurrences, but there have been none so far.

Hemorrhoidectomy has lagged behind most operative procedures in technic, as exemplified by inadequate exposure, indiscriminate excision of tissue and poor control of hemorrhage. Practically no attempt has been made to lessen the pain of this procedure, and, for this reason, patients have rightly come to regard it with dread. Every one but the patient considers it a minor operation and tends to minimize the discomfort. Patients regard it as a catastrophe, and they have frequently telephoned to cancel their reservations for operation after their friends had told them what they had gone through. There are no more appreciative patients in one's practice than those who have been led to believe that they have to endure an ordeal and who find that they can have the necessary operation with practically no discomfort.

PERIARTERIAL INFILTRATION IN DIAGNOSIS AND TREATMENT OF MIGRAINE

EXPERIMENTAL AND CLINICAL EXPERIENCES WITH EUCUPINE AND
PROCAINE HYDROCHLORIDE

REYNOLD PATZER, M.D.; VINCENT DERBES, M.D., AND HUGO ENGELHARDT, M.D.
NEW ORLEANS

Clinicians have long suspected that migraine may be mediated through involvement of the cranial arteries. Many patients have discovered that pressure on the particular artery supplying the painful area will ameliorate the pain. Furthermore, Cushing¹ commented on the striking dilatation of the temporal arteries and veins seen during an attack of migraine. It remained for Wolff² and his co-workers to establish this relationship. In a series of experiments they were able to show that in many cases of migraine the fundamental difficulty was vascular dilatation. They demonstrated that changes in the intensity of headache are related to changes in the amplitude of pulsations in the cranial arteries, chiefly the branches of the external carotid, i. e., the superficial temporal and the occipital. Mechanical experimental distention of the superficial temporal artery by increasing the intravascular pressure produced pain of a migrainous type. It seems probable, however, that pial and cerebral vessels are also implicated at times. According to Wolff,³ this is especially true when the headache is localized behind or in the eye or in the occipital or suboccipital region. In the majority of patients, the attack is localized to the frontal, temporal or occipital regions. Other variants include pain which seems to emanate from the back teeth or pain in the antral regions. Wolff² has attributed these pains to dilatation and distention of the middle meningeal and internal maxillary arteries and the trunks of the external and common carotid arteries. He has pointed out that there is a second mechanism of pain, involving sustained contraction of the muscles of the scalp and neck, during an attack of migraine. These muscles are made to contract reflexly by pain in the head, and the muscular spasm itself is painful

if it is continuous for any period. Measurements have indicated that varying amounts of increased muscle tone accompany the migrainous seizure. Wolff² has attributed the failure of relief to persistence of such contractions, although such drug as ergotamine tartrate may have constricted the dilated vessel responsible for the attack. It must be said, however, that other mechanisms may produce the headache. Reference may be made to a case observed by Goltman.⁴ A woman had had migraine, meeting all the diagnostic criteria, since childhood. Because of ophthalmologic and roentgenographic observations suggestive of brain tumor, she was subjected to exploratory craniotomy. At operation the dura was seen to be tense and the blood vessels dilated. On puncture, a quantity of fluid escaped under pressure from the dura. Further examination revealed the absence of tumor. After the wound had healed, a defect in the skull persisted. There was normally a definite depression in this region but during attacks of migraine this disappeared to be replaced finally by a visible and palpable elevation. This process consistently followed the ingestion of certain foods, especially wheat. It is probable that migraine is in reality a symptom complex which may be caused in yet other ways than the two just described. In the majority of cases, nevertheless, it is due to arterial vasodilatation, and patients whose headache is caused by involvement of the superficial temporal artery may obtain immediate and, at times, dramatic relief from local analgesics.

Because of its prolonged action it was thought that eucupine (isoamyldihydrocupreine) might prove useful in periarthral infiltration for the relief of migraine. Of some historic interest is the fact that this drug was uncovered in a search for an efficient antiseptic. In 1912 Morgenroth reported that this relative of quinine is a power-

From the Departments of Surgery and Medicine, Tulane University of Louisiana School of Medicine and the Ochsner Clinic.

1. Cushing, H.: *The Special Field of Neurological Surgery*, Cleveland M. J. 9:827-863, 1910.

2. Wolff, H. G.: *Headache—Mechanisms and Differential Diagnosis*, Clinics 2:1394-1426, 1944.

3. Goltman, A. M.: *The Mechanism of Migraine*, J. Allergy 7:351-355, 1936.

4. Morgenroth, J., and Ginsberg, S.: *Ueber die Wirkung der China-Alkaloide auf die Cornea*, Ber. klin. Wchnschr. 49:2183, 1912.

ful germicidal agent for the disinfection of ulcers or wounds.

Manheim and Marks⁵ cited Sollmann as stating that the action of eucupine is about forty times that of phenol in destruction of pyogens in a twenty-four hour culture. Bieling⁶ found that pyogenic organisms were destroyed in solutions of eucupine in concentration of 1:10,000. Its use for antisepsis led to the observation of its analgesic property, which is twenty to twenty-five times greater than that of cocaine. Reference to the structural formulas will show that eucupine is a quinoline derivative and so not related chemically to the benzoyl ester anesthetics, such as procaine (fig. 1). The toxicity of eucupine is low; Kilbourne⁷ found the minimum lethal dose for the rabbit to be 0.15 Gm. for each kilogram of body weight. As he pointed out, if man were equally susceptible and if water intoxication were disregarded, the amount of clinically effective anesthetic solution required would be about 3 gallons (11.4 liters). It is neither desirable nor

cedures about the head, neck and face. The solutions did not cause tissue reaction or disturbance in wound healing.

EXPERIMENTS ON ANIMALS

Eucupine with procaine would appear to be ideal for infiltrative anesthesia, inasmuch as it conforms to Braun's⁹ postulates. This surgeon predicated that local anesthetics should be (1) useful in quantities far below the toxic dose, (2) soluble in water; (3) stable to sterilization, (4) compatible with epinephrine and (5) nonirritating to tissues. Up to the present time, there has not been developed a good method for measuring tissue irritation caused by local anesthetics. One of the oldest methods consists in injection of the test solution into a rabbit's ear to determine whether a slough would result. Kilbourne⁷ has shown that this method lacks delicacy. A second method requires the instillation of the solution into the conjunctival sac of the experimental animal. The conjunctivitis produced by irritant solutions does not have a sharp end point and measures only the topical effect. A third method, of definite value, measures the hemolytic action of the solution to be tested. A strict parallelism between the action on red cells and on tissue cells does not exist. The dermal wheal test has advantages but may be criticized in that the dermal layers can stand stronger irritants than the subcutaneous layers and, further, the amount of fluid used is not comparable with clinical quantities. The same general objections apply to the intradermal test on rabbits, which is, nevertheless, an extremely sensitive test.

We feel that the method used in this work is a better one than any of those heretofore available because the results of the unknown infiltrating anesthetic solution can be compared with results of procaine. Procaine hydrochloride solution is considered by many physicians to be the ideal infiltrating anesthetic. Subcutaneous injections with the test solutions were made in dogs. The subcutaneous areas were characterized by copious adipose tissue and poor blood supply, factors which favor sloughing. Furthermore, large amounts of fluid can be injected, and the injections can be made in different places, permitting sections to be removed seriatim.

One dog was used for each solution. Fat, healthy dogs were shaved. Nine injections of the dilution were made on either side, 4 cc. being deposited in each subcutaneous site, which was identified by painting the overlying skin with gentian violet medicinal. After the injection, a biopsy specimen was taken every four

9. Braun, H.: Experimentelle Untersuchungen und Erfahrungen über Infiltrationsanästhesie, *Arch. f. klin. Chir.* 57:370-403, 1898.

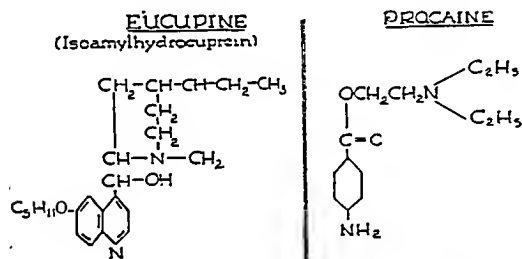


Fig. 1.—Structural comparison of eucupine with procaine.

advisable to use a solution of greater strength than 0.2 per cent; the drug should be protected from light while stored, but it is stable otherwise and can be autoclaved without deterioration. Precipitation occurs when it comes into contact with alkalis. It has, therefore, been suggested that boiled syringes be rinsed with distilled water prior to being filled with eucupine. In 1926 de Takats⁸ reported the use of eucupine (1:1,000) in combination with tutocaine hydrochloride in operations which included repair of hernias, thyroidectomies and minor surgical pro-

5. Manheim, S. D., and Marks, M. M.: Eucupin (Isoamylhydrocupreine) as a Local Anesthetic in Proctologic Surgery and in the Treatment of Pruritus Ani, *Am. J. Surg.* 39:86-94, 1938.

6. Bieling, R.: Ueber die Desinfektionswirkung von Chinaalkaloiden auf pathogene Bacillen, *Biochem. Ztschr.* 85-86:188-211, 1917.

7. Kilbourne, N. J.: Local Anesthetics Producing Prolonged Anesthesia: Elimination of Pain After Rectal Operations, *Surg., Gynec. & Obst.* 62:590-604, 1936.

8. de Takats, G.: Prolongation of Local Anesthesia, *Surg., Gynec. & Obst.* 43:100-105, 1926.

hours for the next seventy-two hours. The wounds were closed with a continuous cotton quilt suture. At the end of seventy-two hours and again at the end of a week, healing of the suture line was observed, notice being taken of infection, induration or discharge. The specimens which had been removed were placed in 10 per cent solution of formaldehyde and later stained with hematoxylin and eosin.

In these experiments, three solutions of eucupine were used: 0.2 per cent eucupine in 1 per cent procaine hydrochloride, a solution in concentration greater than that used clinically (dog A); 0.066 per cent eucupine in 1 per cent procaine hydrochloride, the clinical solution (dog B), and 0.0066 per cent eucupine in 1 per cent procaine hydrochloride, a solution in lesser concentration than that used clinically (dog C). The results obtained with these solutions were compared with the results obtained with the following three procaine hydrochloride solutions: In dog D a 2 per cent solution of procaine hydrochloride in isotonic solution of sodium chloride was employed; in dog E a 1 per cent solution of procaine hydrochloride in isotonic solution of sodium chloride was used, and in dog F a 0.5 per cent solution

of 27.7 per cent showed a serous discharge. The dogs into which the procaine injections had been made showed gross infection ranging from 22 per cent to 55.3 per cent of the wounds, and maximum of 38.8 per cent showed serous discharge, which is considered by most surgeons to be an infected wound. These results are not surprising when it is recalled that eucupine was first introduced as an antiseptic. In dog A gross edema was present in four, eight and twelve hour specimens; in dog B gross edema was present in the four and eight hour specimens, and in dog C gross edema was present in four and twenty eight hour specimens. However, there was no edema in the specimens of dogs D, E and F. There were no sloughs. At the end of seventy-two hours, retention of sutures and primary healing occurred as follows: dog A, 94.4 per cent

TABLE 1.—Summary of Protocols for Dogs

Dog	Maximum Anesthesia, Hr.	Presence of Wound Edema	Wound Slough, %	Wounds Infected at End of 72 Hours, %	Wounds Grossly Infected at End of 1 Week, %	Healing by Primary Intention Sutures Retained at End of 72 Hours, %	Healing by Primary Intention Sutures Retained at End of 1 Week, %	Wounds Healed at End of 5 Weeks, %
A	48	Gross edema in 4, 8 and 12 hour specimens	0	5.5	42.8	94.4	50	94.4
B	64	Gross edema in 4 and 8 hour specimens	0	11.0	50	89.0	50	94.4
C	64	Gross edema in 4 and 28 hour specimens	0	27.7	77.7	72.3	22.2	94.4
D	None at end of 4	0%	0	55.3	72.2	83.5	27.7	77.8
E	None at end of 4	0%	0	22.2	77.7	77.8	22.2	100.0
F	4	0%	0	44.4	55.5	89.0	44.4	89.0

procaine hydrochloride in isotonic solution of sodium chloride was employed.

In table 1 are summarized the results of the experiments. It will be seen that the maximum analgesia was obtained in each instance, lasting in dog A (the first solution) a maximum of forty-eight hours, and in dogs B and C, a maximum duration of sixty-four hours. In dogs D, E and F, as would be expected, no protracted analgesia was obtained. Naturally, it was difficult to determine the absolute degree of analgesia present, but, in order to obtain some degree of comparison, we graded the degree as follows: 4 plus, dogs did not move or make a sound; 3 plus, dogs moved a little; 2 plus, dogs moved and whined; 1 plus, dogs moved more vigorously and whined; 0, dogs struggled and howled. The dogs into which the eucupine had been injected showed a much lower incidence of infection at the end of seventy-two hours, as none of the wounds were grossly infected, and a maximum

of dog B, 89 per cent, and dog C, 72.3 per cent whereas in dogs D, E and F the percentages were 83.5, 77.8 and 89 respectively. At the end of one week, in dogs A, B and C the sutures were retained and healing by primary retention ranged from 22.2 per cent to 50 per cent, as compared with 22.2 per cent to 44.4 per cent in dogs D, E and F. At the end of the fifth week (which was the end of the experiment), 94.4 per cent of the wounds of those dogs into which eucupine had been injected had healed, as compared with 77.8 per cent to 100 per cent in the wounds of the dogs with the procaine injections. Edema appeared more often as a result of the eucupine solutions than from the procaine solutions. On the other hand, the incidence of retention of sutures and primary healing was much lower in the latter series, as would be anticipated from the larger amount of wound infection. It should be mentioned that the dogs in which procaine had been used licked their wounds more often than

those in which eucupine had been injected. From these experiments, it would appear that eucupine solutions may be employed subcutaneously in quantities of 4 cc., with little chance of slough and less chance of infection. These amounts are far larger than are required in periarterial infiltration for the relief of migraine.

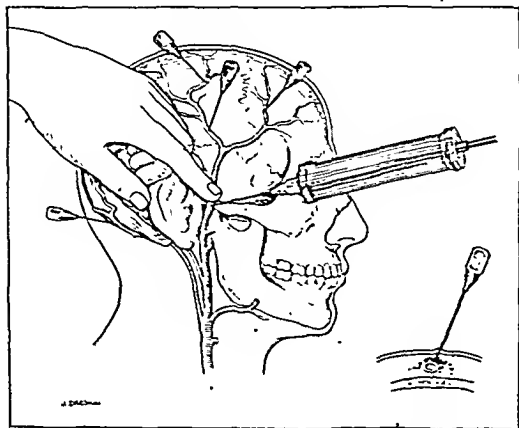


Fig. 2.—Technic of periarterial infiltration with eucupine and procaine.

selected cases. Nausea and vomiting which accompany many of the more severe attacks preclude oral therapy. Certain persons cannot take ergotamine tartrate, either because of the retching which it causes at times or because repeated use of this drug is known to cause ergotism, manifested at first by paresthesias, and later gangrene itself may supervene. The pain may persist because of contraction of skeletal muscles, even though the ergotamine removes the primary cause of the headache. Infiltration of these muscles will afford relief. This procedure is diagnostic in two respects: First, the clinician can convince himself that a particular case is due to arterial vasodilatation and, second, if ligation is contemplated,¹⁰ it predicts the amount of benefit that would accrue from severing a given artery. Infiltration is not meant to replace conventional methods of treatment. Migraine produced by certain foods unquestionably occurs. These foods must be identified by elimination diet, food diary or leukopenic index, for cutaneous tests are notoriously unreliable to detect allergy to food.

TABLE 2.—Illustrative Cases

Patient	Age	Sex	Duration of Symptoms	Frequency of Attacks	Comment
V. J. D.	32	M	26 years	Twice a week	Infiltration right temporal 7/21/44, 7/31/44 and 8/3/44; relief for two months followed by return of attacks
J. P. L.	40	F	As far back as can remember	With each menses	Infiltration of right temporal artery produced such marked relief that patient fell asleep on table
M. M.	38	F	15 years	Twice a month	Pain present in occipital region and in eyeball; infiltration of no aid
R. P.	38	M	16 years	Almost constant	After four infiltrations headaches became much milder and practically disappeared
M. Z.	24	F	1 year	With each menses	Prior to infiltration required 2 weeks rest in bed with each headache; after, no rest in bed required

CLINICAL EXPERIENCE

The technic of infiltration is simple (fig. 2). The superficial temporal artery of the involved side is located external to the zygoma, and approximately 2 cc. of 0.1 per cent eucupine in 1 per cent procaine solution is injected. Often it is necessary to inject subsidiary painful points which are discovered by palpation (fig. 2). In those instances in which accessible branches alone are involved, relief is striking. At times, especially when the pain is referred into the eyeball or along the distribution of the internal maxillary nerve, the procedure is not effective. Obviously, the middle meningeal arteries cannot be reached by this maneuver.

We believe that periarterial infiltration is a definite adjunct in the treatment of migraine in

These are time-consuming procedures, and while they are being employed attacks will continue.

In spite of its relationship to quinine, a drug notorious for producing the gamut of sensitization phenomena, instances of allergy to eucupine rarely occur, and no cases have been encountered by us. On the other hand, two of us (V. D. and H. E.),¹¹ in a critical evaluation of sensitivity to local anesthetics, concluded that safe dosage levels have not been established for any of these drugs.

10. According to Dr. Samuel B. Nadler in 5 instances of paroxysmal temporal headaches abolition of attacks has apparently followed ligation and section of the temporal artery.

11. Derbes, V. J., and Engelhardt, H. T.: Deaths Following the Use of Local Anesthetics in Transcricoid Therapy: A Critical Evaluation. *J. Lab. & Clin. Med.* 29:478-485, 1944.

One can determine a quantum which is tolerated by the majority of persons, but there will be persons who will be sensitive to even the smallest doses.

Table 2 shows the results obtained in illustrative cases in which the patients were treated by periarterial infiltration with eucupine in solution of procaine hydrochloride. In general, the results were beneficial in two distinct ways. In the first place, the majority of patients had immediate relief, though failures were encountered. In the second place, the frequency of attacks was decreased as a rule. It is too early to state the duration of the lessening of frequency of seizures

by this method, but it is not unlikely that it will last six months or longer. It must be mentioned that edema and some soreness are present after the injections and may last twenty-four hours or longer.

SUMMARY AND CONCLUSIONS

An adjunctive procedure for the treatment of selected cases of migraine, consisting in periarterial infiltration of the affected vessel with eucupine and procaine hydrochloride, has been developed. Experimental and clinical observations seem to indicate that the results are beneficial.

PNEUMOTHORAX RESULTING FROM A DISSECTING GASTRIC ULCER

REVIEW OF THE LITERATURE AND REPORT OF A CASE

PERRY B. HUDSON, M.D.

Senior Resident in Surgery, Sibley Memorial Hospital

LENDALL C. GAY, M.D., AND HOWARD E. NEWMAN, M.D.

WASHINGTON, D. C.

In reporting any unusual case history it is doubtless wise to be conservative in claiming that such a case is unique. The case report included in this paper is in its morbid anatomic data unlike any of the several similar case reports of acquired gastrothoracic fistula gleaned from the medical literature available at the Army Medical Library (the Library of the Surgeon General).

A total of 25 authentic reported cases of gastric ulcer which subsequently invaded the structures above the diaphragm were found.¹ It is interest-

ing to note that 21 of these cases were reported before 1900, the reason probably being that since that date laparotomy immediately on the diagnosis of ruptured peptic ulcer has become a routine surgical procedure. Even before 1900 Fenwick stated that there had been only 1 case of perforation of the diaphragm by a gastric ulcer at the London Hospital during forty years.² Subdiaphragmatic abscesses following ruptured peptic ulcers are therefore now highly unusual, as are the sequelae, such as gastrothoracic fistulas. In each of the 25 collected cases there was soiling of the peritoneal cavity prior to thoracic violation. In most of these cases subdiaphragmatic abscess preceded diaphragmatic penetration, and in all of them the stomach was firmly adherent to the inferior surface of the diaphragm. In every case, the muscle of the diaphragm was gradually eroded by a long-standing chronic gastric ulcer.

From the Department of Surgery, Sibley Memorial Hospital.

1. (a) Aufrecht, E.: Ein in die Lunge durchgebrochenes Magengeschwür, *Berl. klin. Wchnschr.* 7: 251, 1870. (b) Günsburg, F.: Zur Kritik des Magengeschwürs, insbesondere des perforirenden, *Arch. f. physiol. Heilk.* 11:516, 1852. (c) Heubner, O.: Ueber einen seltenen Fall von indirecter Magenlungenfistel, in Folge eines perforirenden Magengeschwürs, *Arch. d. Heilk.* 12:193, 1871. (d) von Kogerer: Pyopneumothorax sinister es ulcère ventriculi perforante, *Prag. med. Wchnschr.* 15:315, 1890; (e) Le Noir: Perforation de l'estomac, *Bull. Soc. anat. de Paris* 65:248, 1890. (f) Müller: Spulwürmer in der Pleurahöhle; Pneumothorax; Tod; Memorabilien, *Monatsh. f. rat. Aerzte* 17:448, 1872. (g) Bohm: Lister's Method of Treating Abscess, *Wien. med. Presse*, 1869, p. 990. (h) Sicherer, cited by Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcer, New York, Oxford University Press, 1929. (i) Saxinger, cited by Hurst, A. F., and Stewart, M. J.: Gastric and Duodenal Ulcer, New York, Oxford University Press, 1929. (j) Brenner, F.: Perforation eines runden Magengeschwürs in den linken Herzventrikel, *Wien. med. Wchnschr.* 31:1309, 1881. (k) Bränniche, A.: Et sjældent tilfaelde af ulcus perforans ventriculi, *Hospitalstid.* 5:697, 1887. (l) Siebert, A.: Zur Lehre von der umschriebenen Magen durch Locherung und Magenerweichung, *Wchnschr. f. d. ges. Heilk.*, 1842, p. 465. (m) Starcke, F.: Ulcus ventriculi rotundum; Perforation nach der Peritonealhöhle, in der Leber und in dem linken Pleurasack, *Deutsche Klinik* 22:355, 1870. (n) Guttmann, P.: Pneumopericardium, entstanden durch Perforation eines runden Magengeschwürs in den Herzbeutel, *Berl. klin. Wchnschr.* 17:221, 1880. (o) Rosenstein, S. S., in Ziemssen, H.: *Handbuch der speziellen Pathologie und Therapie*, Leipzig, F. C. W. Vogel, 1876, vol. 6, p. 62. (p) Tillmanns, H.: Ueber die Communicationen des Magendarmcanales mit der Brusthöhle und über subphrenische Kothabscesse, *Arch. f. klin. Chir.* 27:103, 1881-1882. (q)

Chiari, H.: Fall von Perforation eines runden Magengeschwürs in den linken Herzventrikel, und Demonstration des bezüglichen Präparates, *Wien. med. Bl.* 3: 568, 1880. (r) Oser: Ein Fall von Perforation eines runden Magengeschwürs in das linke Herz, *ibid.* 3: 1317, 1880; cited by Fenwick and Fenwick.² (s) Ransom, W. B.: A Case of Pyopneumothorax from Perforation of Gastric Ulcer, *Lancet* 2:1285, 1899. (t) Sturges: Air Entering the Pleura, Not from the Lung; Hydropneumothorax; Partial Recovery, *ibid.* 1:196, 1874. (u) Finny, J. M.: Ulcer of the Stomach, Opening into the Left Ventricle of the Heart, *Brit. M. J.* 1:1102, 1886. (v) Cooper, E. A.: A Case of Perforated Gastric Ulcer with Bilateral Subphrenic Abscess and Broncho-Pleural Fistula, *Canad. M. A. J.* 50:356, 1944. (w) Friedenwald, J.: A Case of Perforated Gastric Ulcer with Abscess Formation: Perforation Through the Lung, with Spontaneous Recovery, *Am. J. M. Sc.* 158:179, 1919. (x) Tauton, J., and Grenier: Ulcère de l'estomac; perforation de la rate, du diaphragme et du poumon par propagation; hématoméses répétées; transfusion sanguine; mort, *Progrès méd.* 29:154, 1913. (y) Tylecote, F. E.: A Note on Perforations of Gastric Ulcers into the Heart Itself, with Report and Photograph of a Case, *Lancet* 2:1613, 1913.

2. Fenwick, S., and Fenwick, W. S.: *Ulcer of the Stomach and Duodenum*, London, J. & A. Churchill, 1900.

Perforation by a peptic ulcer is unusual before the age of 25 years or after 50.³ Ulcerations at the extreme cardiac end of the stomach are usually multiple; they are less than 4 cm. in diameter⁴ and are situated on the anterior aspect.⁵ Of all gastric ulcers, only 7.1 per cent occur in the extreme cardiac portion.⁶

Fenwick² summarized the 21 cases occurring prior to 1900 as follows:

Location	No. of Cases	Ruptured into			
		Pleura (Left)	Mediastinum	Heart	Pericardium
Fundus	6	5	0	0	1
Lesser curvature (cardiac end)	15	6	1	4	4
		11	1	4	5

The 4 cases reported between 1900 and 1944,⁷ as seen in a similar comparison, reveal:

No. of cases	4
Rupture into	
Pleura (left)	3
Mediastinum	0
Heart	1
Pericardium	0

REPORT OF CASE

E. B., a 69 year old white man, a merchant, was admitted by ambulance to Sibley Memorial Hospital for the first time at 1:45 a. m., Dec. 16, 1944.

The routine history on admission revealed a chief complaint of severe epigastric and general abdominal pain. At 7 p. m. the night before admission the patient had several large watery stools and vomited three times in succession; the third emesis was accompanied with the sudden onset of pain in the left upper quadrant of the abdomen. This pain was described as being constant, of a boring character and radiating straight to the back but not down the legs or in any other direction. This entire process consumed the six hours preceding hospitalization. The patient's past history revealed what he described as "indigestion," characterized by vague distress in the upper part of the abdomen. He had been treated elsewhere for this condition for approximately fifteen years, with slight success. There was no clearcut history of ulcer or gallbladder disease, and the patient had been subjected to no surgical operations.

Physical examination on admission revealed a well nourished white man with severe distress in the upper abdominal region, who had the outward appearance of beginning shock. The temperature was 99 F. (rectal); the pulse rate, left and right, and the heart rate were

84 and regular; the blood pressure was 160 systolic and 90 diastolic. The patient would lie on his right side only, with the legs flexed on the thighs and the thigh on the abdomen. There was what appeared to be hemoptysis of mild degree. The patient was mentally somewhat confused, probably because of pain and impending shock. Examination by systems revealed normal head and neck. The systems of the eye, ear, nose and throat were normal except for an artificial right eye. The chest was somewhat emphysematous but on physical examination was normal. The lungs were clear and resonant and the heart normal to percussion and auscultation. The abdomen was normal in contour; not visibly distended, and revealed no hernias. There was considerable involuntary rigidity of the entire abdomen and moderately severe tenderness generally. Rebound tenderness was not helpful to the diagnosis. There was no evidence of fluid or palpable mass. Inguinal and rectal examinations gave negative results. The extremities were pale and cold. Neurologic examination showed no abnormalities.



Fig. 1.—Roentgenogram of the chest (portable film). The bony thorax is normal; the cardiac shadow is shifted to the right, and there is a partial collapse of the left lung, due to pneumothorax, with approximately a 50 per cent expansion of the left lung. The right lung is cloudy, and there may be an early bronchopneumonia in this area. The right leaf of the diaphragm is normal and the costophrenic angle clear. The left leaf of the diaphragm is obscured. The possibility of fluid on the left cannot be determined owing to the fact that the patient was not upright at the time the film was taken.

The conclusion was: pneumothorax of the left side with approximately 50 per cent expansion of the lung; shift of the mediastinum to the right and possible early bronchopneumonia of the right lung.

Laboratory studies revealed the urine to be essentially normal. The hemoglobin level was 83 per cent (Dare New System); erythrocyte count, 4,550,000 per cubic millimeter, and leukocyte count, 1700 (repeated for confirmation). The differential white blood cell count showed polymorphonuclear leukocytes 69 per cent, lymphocytes 21

3. Williams, H., and Walsh, C. H.: Treatment of Perforated Peptic Ulcer, *Lancet* 1:9, 1930.

4. Alvarez, W. C., and McCarty, W. C.: Sizes of Resected Gastric Ulcers, *J. A. M. A.* 91:226 (July 28) 1928.

5. Bockus, H. L.: *Gastroenterology*, Philadelphia, W. B. Saunders Company, 1943.

6. Portis, S. A., and Jaffe, R. H.: A Study of Peptic Ulcer Based on Necropsy Reports, *J. A. M. A.* 110:6 (Jan. 1) 1938.

7. Cooper.¹⁷ Friedenwald.¹⁸ Tauton and Grenier.¹⁹ Tylecote.¹⁷

per cent and monocytes 1 per cent. The Schilling index was: young forms, 1 per cent; band forms, 60 per cent (mostly stab forms), and segmented forms, 8 per cent. A blood smear showed no abnormal elements.

The diagnosis on admission was undetermined.

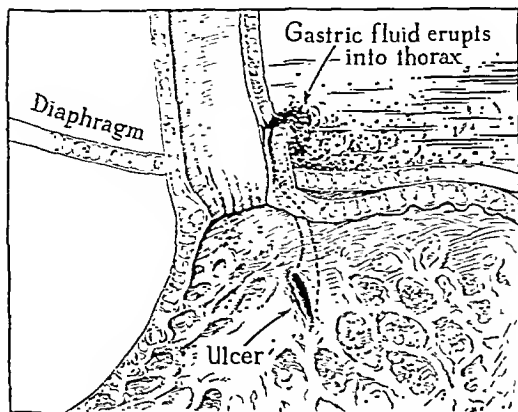


Fig. 2.—Drawing showing location of the ulcer and the method of dissection and rupture into the left pleural cavity without soiling of the peritoneal cavity or erosion of the diaphragm.

It was felt that the patient might have any one of several acute surgical and medical conditions. No clinical impression was strong enough to warrant laparotomy; therefore, a policy of watchful waiting was decided on.

Clinical impressions by various consultants, in order of probability, were: (1) mesenteric thrombosis, (2) ruptured peptic ulcer, (3) dissecting aortic aneurysm, (4) coronary occlusion.

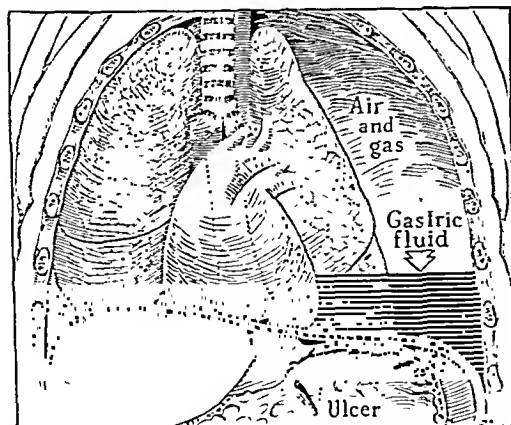


Fig. 3.—Drawing showing hydropneumothorax of the left side at the time thoracentesis was performed.

The course of the disease was most unusual. The abdominal rigidity rapidly decreased until six hours after admission it was slight. The tenderness followed a similar pattern. The temperature rose rapidly from the initial level of 99 F. (rectal) to 105 F. (rectal) six hours later, during which time the blood pressure fell

from an initial reading of 160 systolic and 90 diastolic to 90 systolic and 50 diastolic. At 8 a. m., six and one-quarter hours after admission, the patient, by then semicomatose, began to have severe dyspnea and cyanosis of sudden onset. The dyspnea, it soon became apparent, was accompanied with shifting of cardiac dullness and of the trachea to the right, with all the other classic physical signs of pneumothorax of the left side.

These physical signs were confirmed by roentgenographic studies (fig. 1). When it became obvious that the patient required thoracentesis, a short 13 gage needle was inserted into the sixth intercostal space at the left midaxillary line, with the patient lying on his right side. Immediately after the needle entered the pleural cavity, 200 cc. of thick brownish fluid was withdrawn, followed by 1,150 cc. of air or gas. Respiration immediately improved. Nasal administration of oxygen and other supportive measures were employed, but with a consistently poor ultimate reaction.

The temperature rose to a terminal 106 F. (rectal), and the patient died at 4:25 p. m., fourteen and one-half hours after admission to the hospital.

Laboratory examination of the fluid removed from the chest at thoracentesis revealed free hydrochloric acid, particles of food, occult blood and various bacteria, which were grown subsequently on culture. It was clearly shown to be gastric contents.

Postmortem examination yielded an anatomic diagnosis of: 1. Gastric ulcer of the posterior aspect of the cardiac end of the stomach with erosion into the wall of the stomach and into the wall of the esophagus, causing dissection of the wall with perforation and spilling of gastric contents into the left pleural cavity (fig. 2). There was no peritoneal inflammation or adhesions. 2. Pneumothorax (clinical) of the left side (fig. 3). 3. Cardiovascular-renal disease with (a) mild left ventricular preponderance; (b) atheromatosis of the ascending aorta with plaque formation of the coronary arteries; (c) nephrosclerosis, arteriolar type. 4. Terminal hypostatic congestion of all the thoracic and abdominal viscera, with partial collapse of the lower lobe of the left lung, mild pulmonary edema of the right lung, paralytic ileus and dilatation of the right side of the heart.

It is believed that laparotomy at any time would have been unsuccessful in this case.

SUMMARY

A review of the literature reveals only 25 cases of acquired gastrothoracic fistulas developing from peptic ulcers. In all the previously reported cases the condition was complicated by adhesion of the stomach to the diaphragm and in most of them by subdiaphragmatic abscess. None of the patients in these cases revealed the acute type of ulcer noted in the patient treated by us. None of them had an unsoiled abdominal cavity or the dissection along the coats of the stomach and esophagus described in the report of the autopsy of this patient. It is believed that the morbid anatomy and clinical course in this case are unlike those in cases previously recorded in medical literature.

DESMOID TUMOR

CHARLES C. GREEN, M.D.

HOUSTON, TEXAS

A desmoid may well be termed a pathologic enigma or riddle, and because of its peculiarities there are many differences of opinion as to its cause, pathologic manifestations and treatment. For example, physiologic trauma has been given as the exciting factor in the development of a desmoid, the anterior abdominal wall as its most common location and childbirth as the particular type of physiologic trauma producing it. While 87 per cent of these tumors are found in women and only 13 per cent in men, it is difficult to explain why desmoids are so rare, since in the United States alone there are about 130,000,000 persons, practically all of whom have been brought into the world by the mechanics of parturition alone. But this is only one of many apparent paradoxical statements found in the descriptions of these tumors, and the discussions of their cause.

The name "desmoid" was first used by Mueller, in 1838. It comes from the Greek words *δεσμός*, meaning a "band" or "tendon," and *εἶδος*, meaning "appearance." While Mueller first named this type of tumor, it was MacFarlane who first described it, in 1832. Today it is commonly referred to as a fibroma of the musculofascial layer of the anterior abdominal wall. The desmoid springs from the transverse and the vertical fibers of the posterior surface of the muscle. It is nonencapsulated, grows in the line of least resistance and is elongated or oval. It is composed of white or pinkish fibrous tissue, and it creaks when cut.

Desmoids appear in other localities, but the great majority develop in the muscles and fascia of the anterior abdominal wall. Pfeiffer reported a number of cases, in 72.5 per cent of which the tumor was below the umbilicus, and in 51 per cent of these it was on the right side, in 37 per cent on the left side and in 12 per cent near the midline.

The clinical picture of a desmoid is characteristic, and often it is possible to make a definite diagnosis without the assistance of a pathologist. The picture is that of a hard tumor located in

the anterior abdominal wall, freely movable when the muscles are relaxed but firmly fixed when the muscles are firmly contracted; in a woman it is not attached to the skin, and it develops without pain before she realizes its presence. However, one should not proceed with the excision of one of these tumors without first taking a microscopic section, because the technic of operation is different in case one is dealing with a simple fibroma. For the latter a simple excision suffices, while if the tumor is a desmoid the most extensive excision possible is demanded, one which in some instances all but mutilates the abdominal wall and makes repair difficult.

One of the most interesting features of a desmoid is the fact that unless completely and thoroughly removed, it will recur *in situ* but will not metastasize.

Some authorities state that desmoids do not undergo sarcomatous degeneration. I disagree with this opinion.

REPORT OF A CASE

Mr. J. W. H., aged 65, had had an inguinal hernia on the right side for ten years and had been wearing a truss but had never been operated on. During the last eight or ten months he had had a growth on the lower part of the anterior abdominal wall, which had gradually increased in size until at the time he consulted me he had a tumor extending down to the pubic bone on the inner surface of the external inguinal ring. The tumor was a hard nodular mass, not attached to the skin but firmly attached to the lower end of the right rectus muscle and the pubis. It was neither sore nor tender.

The patient was a well developed, well nourished white man who did not look sick. The blood count showed: red cells, 4,630,000; hemoglobin content, 94 per cent, and white cells, 8,900, with 74 per cent polymorphonuclears, 22 per cent lymphocytes, no monocytes, 2 per cent eosinophils and 2 per cent basophils. Urinalysis showed a specific gravity of 1.015 and an acid reaction; the color was clear-amber; the reactions for sugar, albumin and diacetic acid were negative, and only a few pus cells were observed.

Operation.—With the patient under spinal anesthesia (procaine hydrochloride and pontocaine hydrochloride) an inguinal incision was made, extending from the internal inguinal ring down the course of the cord to the external inguinal ring. The incision was made through the skin and superficial fascia, and then through the fascia of the external oblique muscle. This exposed the hernia and the upper part of the tumor, which was firmly attached to the sac and its contents. A finger

Read at the Fifty-Sixth Meeting of the Southern Surgical Association, Hot Springs, Va., Dec. 6, 1944.

specimen was taken and sent to a pathologist, who reported that the tumor was composed of fibrous tissue undergoing spindle cell sarcomatous changes.

The growth was then removed together with the anterior fascia of the rectus muscle and the cord, cover-

weeks because he was called out of the city. When he finally reported, there had been a return of the growth in the muscle and fascia at the upper part of the wound. He was readmitted and operated on again. At operation a specimen was taken and sent to the pathologist, who



A, appearance (low power magnification) of the compact part of the tumor. Dense fibrous connective tissue and relatively few cells are evident. *B*, section of voluntary muscle close to the main tumor mass. There is separation of muscle fibers by extension of the tumor into muscle. The muscle fibers are atrophic and distorted. *C*, high power magnification of the cellular sarcomatous portion of the tumor. Cells are large, pleomorphic and occasionally multinucleated.

ings, sac and testis but not the muscle. The wound healed, and the man was discharged and told to return to the hospital in a week. He did not return for six

reported that the tumor was a desmoid undergoing sarcomatous changes. After receipt of this report, most of the rectus muscle and all of its anterior and posterior

fascia were removed. This tumor was not attached to the fascia of the external oblique muscle.

It was with difficulty that it was possible finally to close the abdomen by splitting the fascia of the external oblique muscle and lacing it across the abdominal opening. After that the patient received roentgen radiation to the limit of skin tolerance for three weeks.

On thorough roentgenographic examination one week ago there were no signs of metastasis to the lungs or elsewhere, nor were there any signs of local return of the growth. The patient had gained 20 pounds (9.1 Kg.); his health appeared to be good; his blood count was normal and he was going on with his regular work.

Examination of the section of the growth was reported on as follows:

"The section reveals a tumor composed largely of mature fibrous connective tissue with abundant collagen formation. The nuclei are elongated. The connective tissue forms coarse interlacing bundles. In some areas the tumor is moderately cellular with a wavy appearance of the connective tissue fibers. In still other areas the tumor is cellular and anaplastic, having the appearance of rather anaplastic sarcoma. Here the cells vary noticeably in size, shape and staining properties. Some are multinucleated tumor giant cells and have abundant bluish red cytoplasm. They lack definite arrangement except that they tend to approach the arrangement of the surrounding fibrous type of tumor. Voluntary muscle is included in one section and is being invaded by tumor, which separates the striated muscle fibers. Some are isolated and atrophic. A few form rounded protoplasmic, multinucleated masses resembling foreign body giant cells. At the margin of the tumor is a fairly large nerve and a few arteries with moderately thick muscular walls. Still another section reveals numerous inflammatory cells, chiefly lymphocytes, plasma cells and macrophages."

The diagnosis was fibroma of the abdominal wall with sarcomatous changes (malignant desmoid).

I postulate that the anaplastic cells, which are large and frequently multinucleated, cannot readily be transported by the vessels to other parts of the body. Some of these cells do have processes to hold them in place, special stains might show that all still possess processes. This patient will be followed carefully for the few years, as this appears to be a much more cellular type of fibroma than that usually reported.

SUMMARY

Desmoid is a rare type of tumor which is believed to be due to physiologic trauma. In addition to the fact that it contains fibrous tissue with large quantities of collagen, one finds it arising from striated muscle, which differentiates it from other types of fibrous tissue tumors, for example, uterine leiomyoma. It is likely to recur in situ but does not metastasize. In the sections definite sarcomatous changes are shown, many authorities to the contrary notwithstanding.

Dr. Stuart Wallace, professor of pathology at Baylor University Medical College, Houston, Texas, and his staff made available the sections and slides which clearly demonstrated the tissue arrangement of this tumor.

DISCUSSION

DR. JOHN DEJ. PEMBERTON, Rochester, Minn.: Dr. Green's paper is of general interest for several reasons. First, because the cause of these tumors is unknown, second, because of their relatively infrequent occurrence, and, third, because of the extreme rarity of development of malignant changes.

In 1938, Dr. Pearman reviewed all the cases collected at the Mayo Clinic between 1908 and 1938. In 55 of the 77 cases the tumor occurred in the abdominal wall, in the remaining 22 cases the tumor was situated elsewhere in the skeletal muscular system. In these 2 cases the site of the tumor was as follows:

Pectoralis major in.....	5
Muscles about the scapula in.....	4
Rectus femoris in.....	3
Gluteal muscles in.....	2
Sternocleidomastoid in.....	1
Posterior belly of digastric muscle in....	1
Biceps brachii in.....	1
Masseter muscle in.....	1
Other muscles in.....	4

Of the 77 patients, 22 were males and 55 were females.

With regard to causation, Pearman found a history of pregnancy in 33 cases and a history of trauma in 6; the tumor occurred in or about an operative scar in 15 cases. The gross picture of the tumor is that of a densely hard fibroma which shows no tendency to become encapsulated; instead, its periphery merges into the normal muscle fibers. The histologic picture is that of a fairly cellular fibroma occurring in striped muscles. Malignant changes were not found in any cases in this series.

Because of the tendency of these tumors to grow, I feel that in most instances complete excision is the treatment of choice, especially for those in the abdominal wall. However, when the tumor involves certain muscles the loss of which would be attended by severe deformity or disability, I feel that partial excision and radiation therapy is to be preferred.

Recently, I have observed 2 cases in which the deep muscles of the neck, the longus colli muscles, were involved. In neither case was it feasible to excise the entire tumor.

In the cases studied by Pearman there was recurrence of the tumor in 7 per cent of the cases in which the patients were treated by excision and in 12 per cent of those in which the patients were treated by a combination of excision and radiation.

DR. CHARLES C. GREEN, Houston, Texas: There is a wide difference of opinion as to the value of radium for desmoids. The pathologists are about equally divided as to its employment. My position is that until more is known about malignant desmoids I prefer to follow operation by the use of radium or roentgen rays. Desmoids are not primarily malignant, but they are prone to undergo sarcomatous degeneration. The specimen which I presented today is, according to Dr. Stewart Wallace, of Baylor University College of Medicine, rather cellular, and we intend to keep a close watch on it.

AN UNUSUAL ILEOILEAL INTUSSUSCEPTION

MILROY PAUL, M.S. (LOND.), F.R.C.S. (ENG.), M.R.C.P. (LOND.)

Professor of Surgery, University of Ceylon
COLOMBO, CEYLON

This case is reported on account of the unusual type of intussusception encountered and on account of the difficulty which was experienced in deducing the arrangement of the affected coils of bowel from the operative findings.

REPORT OF A CASE

A. G., a boy 4 years of age, was admitted to the Lady Ridgeway Hospital for Children on Feb. 22, 1945 with the diagnosis of intestinal obstruction. The child had been admitted to the Matara Hospital for acute appendicitis on February 1, and the appendix had been removed on that day. At the time of operation, a large number of round worms had been palpated in the small bowel, and the child, who had been making an uneventful con-



Fig. 1.—The ileum ending in an intussusception.

valence, had been given treatment for round worms two weeks after the operation. From this time he had suffered from bouts of acute abdominal pain, had been vomiting several times a day and had not had a stool in spite of the administration of repeated enemas. A diagnosis of intestinal obstruction was made, and at the request of the parents the child was brought to Colombo for operation. He was seen at 12 midnight. He was fast asleep, but showed a definite ladder pattern through the abdominal wall, with visible and palpable peristalsis, coming on every few minutes. The child was emaciated, his skin was dry and inelastic, and his abdominal wall was thin. There was a midline infraumbilical scar. No lump was palpated in the abdomen. He had now awakened, but was quiet and apparently free from pain. A rectal examination showed that the bowel contained masses of mucus but no blood. An enema was returned without feces or flatus.

The child was taken to the operating room in half an hour. A general anesthetic (ether) was used. The peritoneal cavity was opened, a long oblique skin incision

from the right loin to the outer edge of the rectus muscle being used, with splitting of the underlying muscles as in a Mac Burney incision. There was an excess of serous fluid in the peritoneal cavity, and the abdomen was



Fig. 2.—Expulsion of double barreled loop of bowel from neck of intussusception.

filled with coils of small bowel dilated to the diameter of a child's forearm. When the bowel was traced downward, one of the dilated lower coils of ileum was found to be broadly adherent to the scar of the previous operation, but the bowel distal to these adhesions was also greatly dilated. When the dilated ileum was traced farther downward it ended in an intussusception 5 inches

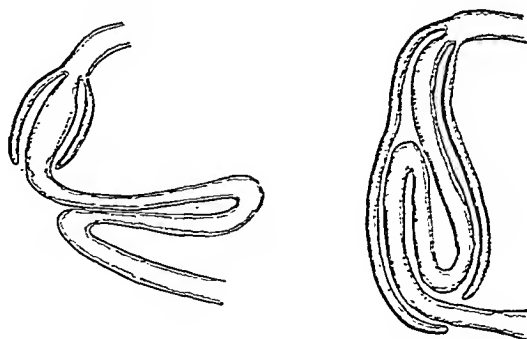


Fig. 3.—Arrangement of bowel in intussusception.

(12.7 cm.) long (fig. 1). The sheath of the intussusception was of normal color, and reduction was commenced by manual pressure backward on the apex of the intussusception. There was a fair degree of resistance to reduction, and even when the neck of the intussusception had been gently dilated with the finger reduction was still difficult. At this stage there was a sudden expulsion of a double-barreled loop of bowel from the neck of the intussusception, the condition being as in

figure 2. The double-barreled loop had been produced by filmy adhesions gluing the adjacent walls together. The rest of the intussusception was reduced without difficulty. The abdominal wound was closed in layers.

The patient stood the operation well, and although his pulse had accelerated to 130 it was of good volume. He made a good recovery from the operation except for a little fever for two days after operation, and he left the hospital on March 14 completely relieved of his symptoms.

COMMENT

It was clear that the intussusception had started after the treatment for round worms, and the increased intestinal peristalsis produced

by this treatment had probably caused the intussusception. The unusual circumstance of finding a double-barreled loop of bowel within the sheath of the intussusception raised the interesting question of the precise arrangement of the bowel in the intussusception. Careful consideration makes it appear that the only possible arrangement is that depicted in the diagrams (fig. 3). According to this view, the condition commenced as an idiopathic ileoileal intussusception, the double-barreled loop of bowel being dragged into the s
it advanced.

REVIEW OF UROLOGIC SURGERY

ALBERT J. SCHOLL, M.D.
LOS ANGELES

FRANK HINMAN, M.D.
SAN FRANCISCO

ALEXANDER VON LICHTENBERG, M.D.
MÉXICO, D. F., MEXICO

ALEXANDER B. HEPLER, M.D.
SEATTLE

ROBERT GUTIERREZ, M.D.
NEW YORK

COMMANDER GERSHOM J. THOMPSON (MC), U.S.N.R.

EDWARD N. COOK, M.D.
ROCHESTER, MINN.

EGON WILDBOLZ, M.D.
BERNE, SWITZERLAND

AND
VINCENT J. O'CONOR, M.D.
CHICAGO

KIDNEY

Anomalies.—Culp¹ observed 6 instances of renal ectopia in a series of 747 cases in which pyelography was performed. In 3 of the 6 cases the patients had simple unilateral ectopia. According to Culp the anomaly was on the left side in 70 per cent of the cases previously reported. In 2 of the cases reported by Culp it was on the right side. The most common site for simple renal ectopia is the true pelvis, but in none of Culp's cases was the ectopic kidney situated in this region. Secondary disease was present in only 1 of the 3 cases of simple unilateral ectopia, but in all 3 there were symptoms referable to a kidney. In 2 cases there was crossed ectopia with fusion. This anomaly usually is found on the right side, but in both of Culp's cases of fused kidney the anomaly was situated on the left side. The lower part of the kidney was ectopic in both instances. One patient had crossed ectopia without fusion; the kidney also was hypoplastic. The right kidney, which was normally placed, had a duplicated pelvis and ureter and was the site of compensatory hyper-

trophy. The patient's only symptom was nocturnal enuresis. Two of the 6 patients also had congenital anomalies of the skeletal system. No genital abnormalities were present, although these were frequent in cases reported in the literature.

The fact that 2 patients had no symptoms referable to the upper part of the urinary tract and no secondary disease and that 2 others had symptoms only while the superimposed disease existed adds support to the contention that the symptoms of patients with ectopic kidneys are usually due entirely to secondary changes. However, the fact that 2 patients had pain that was reproduced by filling the ectopic pelves but did not have secondary disease indicates that the ectopia per se may in some instances be capable of causing discomfort.

Gutierrez² drew attention to double kidney as a potential source of dynamic dysfunction of the urinary system, which may result not only in painful urinary symptoms but also in repeated crises of abdominal pain and gastrointestinal symptoms, owing to the constant insult inflicted on the parietal peritoneum by the adynamic double organ and its crossed double ureters. The anomaly per se, without association of visualized gross pathologic lesions, is responsible for these painful symptoms. Since there is always a

This article has been released for publication by the Division of Publications of the Bureau of Medicine and Surgery of the United States Navy. The opinions and views set forth in this article are those of the writers and are not to be considered as reflecting the policies of the Navy Department.

1. Culp, O. S.: Renal Ectopia: Report of Six Cases, *J. Urol.* 52:420-429 (Nov.) 1944.

2. Gutierrez, R.: Double Kidney as a Source of Impaired Dynamism: Its Surgical Treatment by Heminephrectomy, *Am. J. Surg.* 65:256-267 (Aug.) 1944.

certain degree of nephroptosis, it can be readily understood that the double ureters in crossing (as they usually do) exert pressure on each other and thus interfere with the drainage of the double kidney, from which they issue. As a rule, the dynamism of these crossed ureters becomes impaired, their rhythmic contractions are disturbed and the time of emptying is prolonged. Because of the intricate nerve connections between the kidney and the ureter, on the one hand, and the chief ganglions of the abdomen, on the other, the crises of pain arising in an overfilled ureter and renal pelvis are readily transmitted to the abdominal cavity, where they may give rise to indefinite abdominal pain with nausea and vomiting, and the anomaly frequently is mistaken for appendicitis, especially if the double kidney and the ureters are on the right side. Such symptoms may completely divert the attention from a double kidney as the possible cause of the surgical syndrome.

Admittedly, conservative operation for relief of associated disorders in cases of double kidney was performed even prior to the urographic era, but conservative operation deliberately undertaken solely for correction of the impaired dynamism and faulty mechanics of the double kidney seldom if ever has been carried out. The author stressed the importance of the orthopedic surgical correction of double kidneys. Every patient suffering from repeated attacks of indefinite abdominal pain should be submitted routinely to urologic studies, in order to rule out an anomalous surgical condition of the kidneys. When the physiologic emptying is retarded or incomplete in one or both pelves of the double organ, there is always evidence of a surgical condition. Delayed urograms, made one or more hours after intravenous injection of the opaque substance, are of great value in diagnosis, but an adynamic condition thus revealed should always be confirmed by retrograde pyelography.

Heminephrectomy or partial resection of the double kidney with the corresponding supernumerary ureter appears to be the operative procedure of choice and offers the best prospect of restoration of function and complete disappearance of symptoms. It is as simple and easy to carry out as an ordinary lumbar nephrectomy. This conservative procedure should be followed by nephropexy, to straighten the ureter and secure good drainage from the remaining half of the double organ. Conservation of tissue is imperative whenever feasible. After operation the patient should always have a complete postoperative check-up before leaving the hospital, in order

to determine the anatomic and function of the procedure.

When a double kidney is urographically covered and is associated with painful and dynamic dysfunction, the condition always be considered surgical, even if there is a so-called normal double kidney.

Conroy and Walker³ stated that a solitary kidney constitutes a fairly common anomaly and has an incidence of approximately 1 in 1,000. This anomaly is generally of little clinical recognition most frequently resulting from an incidental investigation. The relative frequency of this anomaly and the finality of error if a single kidney is removed is essential that pyelography be performed in any surgical procedure on the upper pararenal tract. If the anomaly is discovered incidentally and if the solitary kidney is present there is no indication for rejecting the man from military service. From the data available, it is not possible to draw firm conclusions concerning the added hazard that the anomaly may constitute in military life. Conroy and Walker³ said that the hazard is not great.

Smith and Orkin⁴ stated that malformations of the kidneys and ureters are of great clinical importance and account for about 40 per cent of all pathologic conditions of these organs. In a large series of patients (18,460) consecutively admitted to urologic hospitals there were 17 with congenital anomalies. The incidence according to these data would be 1:40, but this is much too low. Since the introduction of retrograde urography the incidence has been found to be 1:27 (3.7 per cent). While the most frequent congenital anomaly is double renal pelvis and ureter, which occurred 97 times, for a clinical incidence of 1:190, the other anomalies occur often enough to warrant attention.

Consideration of the patients in this series shows that the average age was 37 years, that males were affected slightly more frequently than females (the ratio being 250:221) and that the anomaly apparently has no predilection for either the right or the left side. Considered together, unilateral involvement is at least four times as frequent as bilateral involvement.

Although renal anomalies are compatible with a healthy existence, this is the exception rather than the rule, as it occurred in only 17 per cent of the cases. Practically any urologic symptom

3. Conroy, T. E., and Walker, J. H.: Congenital Solitary Kidney: Case Reports and Considerations of Military Significance, *J. Urol.* 53:439 (Jan. 1945).

4. Smith, E. C., and Orkin, L. A.: A Comparative Statistical Study of 471 Congenital Anomalies of the Kidney and Ureter, *J. Urol.* 53:11-26 (Jan. 1945).

may be encountered, but the one most frequently encountered is pain; it occurred in 78.9 per cent of the cases. A further study of symptoms revealed that an anomalous kidney may produce symptoms without the presence of associated renal disease.

Of the series of patients with anomalies only 20.5 per cent showed no associated pathologic changes. This observation illustrates the fact that a malformed kidney is especially prone to disease. Considered together, urinary infection, hydronephrosis and calculus accounted for 89 per cent of the secondary pathologic conditions.

In 138 (29.2 per cent) of the 471 cases open surgical intervention was necessary. Nephrectomy and conservative procedures were employed in about an equal number of cases.

Since anomalous kidneys are especially prone to disease, it is believed that only by early diagnosis and treatment can a good many of the complications be prevented or ameliorated.

Tumors.—Abeshouse and Weinberg⁵ made an analytic study of 63 cases of renal neoplasm and reviewed the literature. Renal neoplasms are more common in men than in women.

Parenchymal renal neoplasms are observed most frequently in the sixth and seventh decades of life, with the exception of Wilms's tumor, which is observed in infancy and early childhood.

The most common initial symptom in Abeshouse and Weinberg's series of cases was painless hematuria. Next in frequency were pain and a tumor mass. Pain occurred in 94 per cent, hematuria in 81 per cent and a tumor mass in 63 per cent of the cases respectively. This triad of symptoms is usually reversed in children with Wilms's tumor and in adults with inoperable tumors. In these patients a mass is the most frequent symptom.

Retrograde pyelography was performed in 56 cases, and a correct preoperative diagnosis based on the pyelographic observations was made in 42 cases. In Abeshouse and Weinberg's clinic greater reliance is placed on retrograde pyelography than on intravenous urography for the diagnosis of renal neoplasm.

The most common urographic observations associated with malignant neoplasm are compression of one or more calices, elongation of one or more calices, distortion or compression of the renal pelvis, displacement of the ureter or the pelvis, dilatation of the pelvis and calcification within the tumor.

In cases of parenchymal neoplasm the characteristic pyelographic changes are compression and elongation or obliteration of one or more calices. In cases of pelvic tumor a filling defect of the pelvis is the most common finding.

In Abeshouse and Weinberg's series of 53 cases in which neoplasms were treated by nephrectomy, there were 4 deaths (7.5 per cent). These deaths occurred after lumbar nephrectomy. This low operative mortality compares favorably with that reported in the past forty years.

Surgical intervention is justifiable in every case of suspected renal neoplasm, despite the relatively low survival rate. Early diagnosis and operation increase the chance of cure.

The following factors influence the prognosis: nature and duration of the symptoms; condition of the patient; type, size and mobility of the tumor; presence of tumor thrombi in the renal vein and the inferior vena cava; metastasis, and type of surgical treatment and of irradiation therapy.

The best results from the standpoint of survival following nephrectomy were obtained in cases of Grawitz' tumor, and the poorest results with operative treatment were obtained in cases of pelvic neoplasms. In cases of Grawitz' tumor a three year cure was obtained in 32 per cent of the cases; a five year cure in 35 per cent; a ten year cure in 20 per cent, and a fifteen year cure in 5 per cent.

McGee⁶ stated that clinically Wilms's tumor has no typical course except that it is insidious in its onset and relentless in its course. The usual train of events is abdominal distention, malaise, constipation, discovery of the tumor, loss of weight, increase in size of the tumor and death from cachexia or intercurrent infection.

McGee reported a case of Wilms's tumor. The patient was a girl aged 20 months who had lost several pounds. The routine urinalysis showed albumin and erythrocytes. On physical examination a suggestive mass was felt in the region of the left kidney. There was no excretion of intravenously injected dye from the left kidney. A nodule was present in the supraclavicular region on the left side. Microscopic examination of this nodule revealed a malignant round cell neoplasm. Roentgen radiation was applied over the left renal area and to a suspected site of metastasis in the neck. There was no response whatsoever, and the condition of the child rapidly became worse. The tumor in the left renal region became more readily palpable, and the patient died two months after the opera-

5. Abeshouse, B. S., and Weinberg, T.: Malignant Renal Neoplasms: A Clinical and Pathologic Study. *Arch. Surg.* 50:46-55 (Jan.) 1945.

6. McGee, H. J.: Wilms Tumor: A Case Report. *J. Urol.* 52:489-491 (Dec.) 1944.

tion. This case was unusual in that the renal tumor was of only moderate size.

Hydronephrosis.—Lowry, Hayward and Beard⁷ stated that in cases in which hydronephrosis is due to obstruction at or near the ureteropelvic juncture symptoms are frequently absent or misleading and the physical findings seldom are pertinent. The obstruction produced by the accessory renal vessels is not always at the ureteropelvic juncture and may be either proximal or distal to this point. Obstruction of the renal pelvis proximal to the ureteropelvic juncture produces a characteristic pyelogram, which is unlike that produced when the vessel crosses at the ureteropelvic juncture. A crescent-shaped deformity is demonstrated by the opaque medium in the portion of the renal pelvis distal to the obstructing vessel. The authors reported a case of giant hydronephrosis (5,100 cc.).

Greene,⁸ in considering the effects of ureteral dilatation on the ureter and the kidney, stated that in normal dogs the time required for indigo carmine to appear in the urine is two to three minutes. In spite of all variations of technic, delineation of the normal urinary tract of dogs by excretory urography is poor; the urinary tract can be visualized satisfactorily by retrograde pyelography. As determined by delayed roentgenography, the renal pelvis will empty itself completely in three minutes.

Moderate dilatation of the ureter of dogs (9 to 11 F.) results in decrease of the rate and amplitude of ureteral contractions, decrease of the rate of transmission of urine down the ureter and proved unilateral visualization of the urinary tract by excretory urography. Wide dilatation of the ureter of dogs (14 to 16 F.) results in ureteral hypertonicity, which acts as a functional obstruction and produces acute pyelectasis and reterectasis. Repeated wide dilatation of the ureter produces permanent hydronephrosis and hydroureter.

The characteristic histologic picture of a hydronephrotic kidney which results from ureteral dilatation is scattered regions of tubular dilatation and collapse. The histologic changes in the ureter which result from dilatation are loss of mucosa, edema of the submucosa, stretching and rupture of the smooth muscle and widespread hemorrhage.

Tuberculosis.—Gutierrez⁹ emphasized the importance of early diagnosis of renal tuberculosis

and the possibility of its complete eradication by surgical treatment when it has reached the operative stage. The profound changes in standards of living produced by the war have increased the incidence of all forms of tuberculosis, and it is reasonable to expect that this increase will be observed in renal as well as in other forms of the disease. It has been abundantly demonstrated from the time of Albarran that in cases of unilateral tuberculosis of the kidney removal of the affected kidney will result in complete cure. In 80 to 90 per cent of cases of renal tuberculosis, which is a blood-borne infection, the disease is unilateral, the original lesion being in the lung; the lymphatics or the bony system, in which it may have become quiescent. So long as the renal lesions remain closed, that is, isolated within the renal parenchyma and expressed only by tuberculous bacilluria, without other symptoms within the urinary tract, they may heal without surgical treatment. Once they have opened into the excretory apparatus, however, no treatment except nephrectomy will be effective. It is these open lesions which constitute tuberculosis of the kidney. By the time a lesion becomes open, the pathologic process is well established; it has destroyed the parenchyma of the kidney and has formed typical caverns, such as are seen in pyonephrosis.

In the surgical management of renal tuberculosis one must also consider the surgical lesions that may involve the ureter and the urinary bladder, which will demand further treatment. Two types of tuberculous ureter can be demonstrated preoperatively: (1) the hydroureter and the megaloureter, in which there is a vesicoureterorenal reflux, and (2) the ureter which is the site of infiltration and severe ureteritis and is so greatly indurated that it can be detected by rectal or vaginal palpation. For both of these types combined ureteronephrectomy by two separate incisions is the procedure of choice. When, however, an advanced lesion of the ureter is discovered in the course of nephrectomy, the lumbar incision should be prolonged to include ureterectomy. This total and radical procedure is simple and assures a permanent cure. It is important to emphasize that if the ureter is not removed in toto when it is tuberculous it may produce a purulent lumbar fistula or persistent cystitis, which will demand secondary ureterectomy. Treatment of a tuberculous ureter of the bladder will be useless if the stump of a tuberculous ureter has not been removed at the time of nephrectomy. In the past many failures

7. Lowry, E. C.; Hayward, J. C., and Beard, D. E.: The Diagnosis of Hydronephrosis Caused by Accessory Renal Vessels, *J. Urol.* 52:492-495 (Dec.) 1944.

8. Greene, L. F.: The Renal and Ureteral Changes Induced by Dilating the Ureter, *J. Urol.* 52:50 (Dec.) 1944.

following nephrectomy have been attributable to this oversight.

In the 10 to 20 per cent of cases in which disease is bilateral, the disease is of two principal types: 1. Only one kidney has undergone destruction of the papillae, calices and parenchyma, while the organ of the opposite side is normal urographically, although the catheterized specimen of urine discloses excretory tuberculous bacilluria. Removal of the destroyed kidney is obviously indicated. 2. The destructive process is far advanced and can be demonstrated in the retrograde pyelograms of both kidneys. In such a case no operation seems to be indicated unless a large pyonephrotic kidney is present. This calls for drainage by a simple lumbar nephrostomy, to relieve symptoms and prolong life.

It is well to emphasize that the sulfonamide drugs have no effect on the tubercle bacillus, and no time should be wasted in their use or in other forms of palliative treatment. After nephrectomy, however, the patient should be submitted for a considerable time to a proper dietetic and hygienic regimen, medical care and rest, preferably in a sanatorium. There will be no permanent cure of renal tuberculosis until the primary focus within the kidney has been removed. The curability after nephrectomy is high; the operative mortality is low. The prognosis on the whole is excellent for a permanent cure.

Renal Operations.—Mathé¹⁰ reviewed 247 consecutive cases in which nephrectomy was performed. It is his opinion that the low mortality and morbidity of nephrectomy can be still further reduced by the judicious choice of the method, based on the individual case. Use of the extraperitoneal approach, careful operative technic and adequate preoperative and postoperative care are important factors.

Malignant lesions of the kidneys demand clamp nephrectomy and removal of the perirenal fat in its entirety. Early clamping of the pedicle minimizes metastasis and produces the highest percentage of clinical cures. When rapid termination of the operation is required because of shock or when friable renal tissues cannot be safely ligated, clamps should be left in place. Secondary hemorrhage never followed their removal in the author's experience.

Clampless nephrectomy is performed whenever it is technically possible to ligate the pedicle, except in cases of malignant lesions, because it is accompanied by less shock and fewer compli-

cations. Subcapsular nephrectomy and, rarely, nephrectomy *par morcellement* are the only methods of extirpating a diseased kidney that cannot be dissected free from surrounding structures. In extremely debilitated candidates for nephrectomy a two stage operation offers the best results. In some instances it has spared the kidney.

Nephroureterectomy is indicated for destructive renal lesions associated with megaloureter, for primary carcinoma of the renal pelvis, for primary carcinoma of the ureter, for calculous and cystic ureteritis and for renal tuberculosis associated with extensive ureteritis. As performed by Mathé, it is aseptic throughout and is as well tolerated as the simpler types of nephrectomy.

Abeshouse¹¹ reviewed 2,298 reported cases in which renal disease was treated by decapsulation, and he reported 10 cases which he had observed personally.

Decapsulation is an operation of unquestionable merit in carefully selected cases. The operation is never curative but only palliative; it restores or improves renal circulation and secretion. From the extensive reports in the literature, it is apparent that definite indications and contraindications have been established for decapsulation in cases of various renal diseases. The two chief indications for decapsulation are progressive oliguria and anuria. Pain and hematuria may also serve as indications for operation in certain selected cases. Decapsulation should not be attempted until appropriate medical treatment has been given a thorough trial. The best results with decapsulation are obtained when the operation is performed early. Poor results not infrequently are due to the fact that the operation is employed as a desperate final measure when the patient is moribund.

Acute glomerulonephritis is ordinarily amenable to medical treatment. However, surgical intervention is indicated in certain cases in which the disease has failed to respond to conservative therapy. Decapsulation should be performed within twenty-four hours after the onset of anuria. Early operation is also indicated in cases of progressive oliguria, increasing edema and rising blood pressure. Pain and hematuria accompanying acute glomerulonephritis and uninfluenced by medical treatment may require decapsulation.

Decapsulation is contraindicated in cases of chronic nephritis (Bright's disease) unless

10. Mathé, C. P.: Evaluation of Different Types of Nephrectomy: Review of 247 Cases, *J. Urol.* **53**:85-96 (Jan.) 1945.

11. Abeshouse, B. S.: Renal Decapsulation: A Review of the Literature and a Report of Ten Cases, *J. Urol.* **53**:27-84 (Jan.) 1945.

there is progressive oliguria or anuria and unless there are superimposed acute nephritic crises.

Decapsulation has yielded excellent results in the treatment of pain (nephralgia) and hematuria associated with acute or chronic glomerulonephritis of the focal or diffuse type which are unaffected by the usual conservative measures.

This procedure is seldom indicated in cases of acute pyelonephritis, in view of the success attending conservative treatment, including sulfonamide therapy.

Uniformly good results are obtained by decapsulation and nephrolysis in cases of chronic perinephritis. After the diagnosis has been established, early operation is advisable, in order to prevent constrictive changes in the kidney and ureter.

Operation is rarely indicated in cases of genuine lipid nephrosis, notwithstanding the good results reported in the relatively few cases in which the operation has been employed. Operation should be restricted to cases of persistent edema and increasing albuminuria or to cases in which recurrent nephritis does not respond to a high protein diet and to thyroid extract.

Excellent results have been obtained by decapsulation in the treatment of resistant pseudo-nephrosis, that is, the nephrotic stage of chronic parenchymatous nephritis.

Decapsulation is contraindicated in the treatment of tubular nephrosis associated with bichloride of mercury poisoning. The best results follow the early and complete removal of the poison from the gastrointestinal tract by gastric lavage and cecostomy in conjunction with intravenous administration of fluids. When oliguria and anuria develop despite these measures, early decapsulation may prove invaluable.

Decapsulation is indicated in cases of persistent oliguria or anuria, following sulfathiazole or sulfapyridine therapy, after presence of calculi or concretions in the pelvis or the ureter has been ruled out by cystoscopy and ureteral dilation.

Early decapsulation has proved an effective method of combating the anuria associated with the post-transfusion type of nephrosis.

Decapsulation alone or in conjunction with denervation has been ineffective in the treatment of hypertension due to primary arterial disease of the kidneys.

Unilateral decapsulation is relatively simple and can be easily carried out through the usual oblique or curved incision within fifteen to twenty minutes.

Dos Santos¹² said that the history of the operative treatment of nephritis reveals how sur-

gical intervention based on an illusory idea or produce excellent results, thanks to an unsuspected mechanism. Harrison's nephrotomy, which first was performed with a view of freeing the renal parenchyma from strangulation, and Edbohl's decapsulation, which was designed to create between the cortex and the fatty capsule an anastomotic network to produce better circulation in the parenchyma, were both based on false ideas. Yet decapsulation is in fact a sound procedure in the treatment of glomerulonephritis but for another reason. This became apparent when Volhard's new conception of anuria in glomerulonephritis proved that operation on the sympathetic nervous system is able to modify the angiospastic component of nephritis by denervating the kidney, at the pedicle, capsule, aorticorenal ganglion or in the splanchnic nerve proper.

All forms of nephritis can be reduced to the common denominator of hematogenous infection of the kidney and their results. Nephritis is essentially an arteriolocapillaritis of the glomeruli with secondary degeneration of the tubules. The results of the progressive ischemia are sclerosis and degeneration of the secretory elements of the kidney, in other words, renal insufficiency. Thus nephritis begins with infection and terminates with uremia. Between these poles there is vascular disease of the kidney, sometimes latent and almost symptomless over a long period. It is in this intermediate phase, in which the lesions are still not very extensive and in which angiospastic symptoms predominate, that operation on the sympathetic nervous system is indicated. In whatever form this type of operation is used, the aim is to achieve active and permanent vasodilatation of the kidney, suppression of the angiospasm and improvement of the circulation and of the nutrition of the epithelial cells.

Painful nephritis and hematuric nephritis show plainly the vasomotor cause of the syndrome. The pain, as a rule, is due to ischemia, and both the pain and the hematuria are relieved by denervation of the capsule. What operative accomplishment in cases of nephritis is suppression of the vasomotor component, through capsule sympathectomy. Results have been highly gratifying and have proved permanent. Sympathectomy is the best means of bringing nutrition to the epithelial cells, of retarding sclerosis, of improving secretory function and of relieving the pain and hematuria by decreasing the degree of hypertension.

12. Dos Santos, R.: The Surgical Aspect of Nephritis, *Arch. españ. de urol.* 1:3-10 (July) 1944.

Renal Hypertension.—Bumpus¹³ reported a case of renal hypertension in which the patient was a man 27 years of age, who had had recurring headache and a systolic blood pressure of 220 mm. Intravenous pyelograms showed a normal functioning, hypertrophied right kidney. No evidence of dye was seen in the left renal area. On cystoscopic examination it was found that catheters could be passed up both the right and the left ureter without obstruction, although the left ureter was smaller than normal. There was no excretion of phthalein from the left side; on the right, excretion was better than normal. A pyelogram of the left kidney showed some dilatation of the calices and pelves. A pyelogram of the right kidney was normal. A nephroureterectomy was performed, and the blood pressure dropped from 220 to 130 mm. The pathologic diagnosis was stenosis of the distal end of the left ureter with associated hydroureter and hydronephrosis. On the eighth postoperative day the patient had a severe attack of dyspnea; he died six days later. During these six days, the value for the nonprotein nitrogen was greatly elevated and the urinary output decreased considerably. Necropsy revealed thrombosis of the remaining right renal artery. The interesting clinical point is that the thrombosis of the remaining right renal artery was sufficient to reproduce the hypertension. The remaining accessory artery permitted enough renal tissue to function so that the fluid balance was well maintained.

URETER

Tumors.—Vest¹⁴ reported 3 cases of primary benign tumor of the ureter. Instead of routine nephroureterectomy, conservative operations were performed. The local tumor and the surrounding ureteral wall were excised so as to preserve the kidney. The preoperative, operative and postoperative observations confirm the impression that the tumors were localized and were benign.

A study of the literature revealed the following facts: The majority of ureteral tumors are malignant. Benign tumors of the ureter do occur. Diagnosis of ureteral tumors is more often not made (but in the future this need not be true). Benign ureteral tumors metastasize rarely, if ever, but sometimes are implanted lower and in the bladder. The majority of benign tumors are not multiple and occur in the lower part of the ureter. Only in rare instances can they be

distinguished from malignant tumors preoperatively. Benign tumors occur as epithelial tumors which show no histologic evidence of malignancy or as polyps made up of benign stroma with a transitional epithelial covering. The treatment of benign tumors reported in the literature has been, in the main, nephroureterectomy, as for malignant tumor. A number of illogical procedures have been carried out.

Vest concluded that urologic surgeons should carefully consider a localized ureteral tumor from the clinical, roentgenologic and pathologic standpoints before destroying the kidney. By so doing, they can occasionally save a needed kidney. Nephroureterectomy is not a routine procedure for all tumors of the ureter. The decision between nephroureterectomy and conservative management should be made by competent urologic surgeons and pathologists. Such conservative therapy in other hands would be most ill advised.

BLADDER

Calculi.—Love¹⁵ reported a case in which a woman passed a large vesical calculus by way of the urethra. There are a few references in the literature to spontaneous passage of calculi through the female urethra. The instances cited include 1 case in which a woman passed two calculi weighing 40 and 105 Gm. respectively and another case in which a woman aged 18 years passed a calculus weighing 4 ounces (115 Gm.), which caused a urethrovaginal fistula.

Vesical calculi in females are usually due to introduction of a foreign body into the bladder. The foreign body becomes coated with phosphates as a result of secondary cystitis. The specimen in the case reported by Love was a primary oxalate calculus, and the stone measured $5\frac{3}{8}$ inches (14 cm.) in circumference and $1\frac{5}{8}$ inches (4 cm.) in diameter. The ability of the female urethra to dilate so that a stone of this size can pass without causing more than temporary disability is amazing.

The patient was referred to the hospital as a woman in labor. She had noticed urinary frequency for some time and had had some abdominal pain and discomfort. Examination revealed a distended bladder. On vaginal examination a hard mass could be felt in the region of the urethra. Further investigation revealed a stone which blocked the urethra. The stone passed voluntarily, and the passage was followed by transient incontinence of urine. The patient did her best to exonerate her physician for his

13. Bumpus, H. C., Jr.: A Case of Renal Hypertension, *J. Urol.* **52**:295-299 (Oct.) 1944.

14. Vest, S. A.: Conservative Surgery in Certain Benign Tumors of the Ureter, *J. Urol.* **53**:97-121 (Jan.) 1945.

15. Love, M.: A Large Vesical Calculus Passed per (Female) Urethram, *Brit. J. Surg.* **32**:323-324 (Oct.) 1944.

erroneous diagnosis of pregnancy by stating that "she felt as if she were giving birth to a hedgehog."

Tumors.—Jewett¹⁶ considered ureterointestinal anastomosis in two stages for carcinoma of the bladder and reported 33 cases. His modification of the operative technic has simplified the procedure. The most important measures to be adopted at the first stage are (1) prophylaxis of adhesions and (2) proper fixation of the sigmoid colon containing the ureter. The second stage includes (1) adequate mobilization of the sigmoid colon containing the ureter, (2) calibration of the intramural ureter, (3) avoidance of tangential cut with the electrode, (4) establishment of an ostium of adequate length and (5) prevention of subsequent leakage from the emerging ureteral stump by treatment with phenol and alcohol and by triple irrigation.

No statement was made in regard to ultimate cure, because in all of the cases of carcinoma of the bladder less than five years had elapsed since total cystectomy was done. The results in Jewett's series of 33 cases, observed during the last four years, demonstrated the soundness of the basic principle involved in two stage ureterointestinal anastomosis. In his last 10 cases, in which the modified technic was employed, only 1 death occurred; this was due to hemorrhage from unrecognized pulmonary metastasis. In properly selected cases uneventful convalescence and subsequent normality of the upper part of the urinary tract are contingent on technical perfection in the practical application of this two stage procedure.

Graves and Thomson¹⁷ stated that total cystectomy for carcinoma is an operation which could be used in cases in which complete excision of the malignant disease may be accomplished by total removal of the bladder itself. Cystectomy should be performed with the intent of cure and under conditions which render cure possible. It should not be selected as a means of palliation when there is obvious spread of tumor beyond the limits of the vesical wall. Graves and Thomson have performed this operation in 28 cases, and they believe that cystectomy is a valuable procedure and that they are well find it employed more often and with

increasingly satisfactory results. The first of the 28 patients was operated on in 1933, the time of writing (1944) 13 of the group were living and free from malignant disease as far as could be determined. The period of survival since cystectomy varied from one month to one and one-half years. Of the last 20 patients operated on since 1939, 11 were living and there was no apparent evidence of recurrent carcinoma.

The indications for cystectomy have become definite and clearcut. First, there should be reasonable assurance, based on every possible form of investigation, including abdominal exploration, that there is no distant metastasis and that removal of the bladder and its adjacent structures will completely remove the vesical tumor. The age and general condition of the patient should be such as to permit him to survive the operation and live to enjoy its benefit for a significant period. Graves and Thomson adopted a tentative upper limit of 69 years for this procedure and hesitated to advise cystectomy for older patients.

Multiple tumors, often of low grade malignancy, call for cystectomy when they involve so much of the vesical mucosa that local resection is impracticable and destruction by electrocoagulation and radium will virtually destroy the bladder itself. High voltage roentgen therapy should not be relied on in most instances as a method of cure. Its use may be attended with actual disadvantage when operation later becomes necessary. This is particularly true of ureterointestinal anastomosis, which may be adversely affected by roentgen therapy, probably as a result of the fibrosis which it produces in the walls of the bowel and ureter.

Extensive infiltrating carcinoma, still confined to the bladder, also is an indication for cystectomy, since radium and roentgen rays usually do not cure tumors of this type and since local excision is equally ineffective in most cases. Tumors of the outlet of the bladder, particularly those which overlie the prostate gland in men, also are an indication for cystectomy. Because electrocoagulation and irradiation sufficient to destroy the growth in this region will seriously impair the usefulness of the bladder, through occlusion of the urethra and destruction of sphincteric function.

Finally, tumors of the trigone demand cystectomy when they occlude both ureters or when they encroach on the ureters so closely that the ultimate occlusion, as a result of disease or of treatment, is inevitable. The successful results of operation for malignant disease of the bladder will depend on the preservation of

16. Jewett, H. J.: Uretero-Intestinal Anastomosis in Two Stages for Cancer of the Bladder: Modification of Original Technique and Report of Thirty-Three Cases, *J. Urol.* 52:536-562 (Dec.) 1944.

17. Graves, R. C., and Thomson, R. S.: Total Cystectomy for Carcinoma, *J. Urol.* 52:448-454 (Nov.)

equate renal function as well as on the cure of the malignant disease.

In order to obtain full information as a basis for selection of the best method of treatment in the individual case of vesical tumor, Graves and Thomson have adopted routine studies which are insisted on before a final evaluation is made. Anemia readily corrected by transfusion may be of little importance; anemia is ominous if it fails to respond to treatment or if it cannot be explained by hematuria alone. Estimations of renal function by excretion of phenolsulfonphthalein and by chemical examination of the blood are a basic necessity. Roentgenologic examinations are made of the thorax, the abdomen and any other region of localized pain. Intravenous pyelograms are important and always should be obtained when renal function has been found sufficiently good to render this procedure safe and informative. The choice of treatment will be greatly influenced by the knowledge thus gained concerning the function of the kidneys and the state of their excretory passages.

The final evaluation with reference to the choice of therapy is made at the time of cystoscopic and rectal examination with the patient under spinal anesthesia. Graves and Thomson regard this routine use of anesthesia as the most helpful advance that they have made in the study of carcinoma of the bladder. The patient is relaxed and comfortable; the surgeon is not hurried and the filling and emptying bladder may be watched at leisure. The nature, site and extent of the tumor may be determined better with the patient under anesthesia than in any other way. More of the bladder is brought into view, and the relations of the neoplasm to the ureteral orifices and the vesical outlet are much more accurately defined than would otherwise be possible.

Most important information with reference to the possibility of cystectomy is obtained by the rectal examination with the patient under anesthesia. One learns in this way the true size of the tumor, its palpability, the degree of its infiltration through the wall of the bladder, the movability of the mass and its distance from the rectum and the lateral walls of the pelvis. One may discover evidence of extension of disease or of local metastasis that lies beyond the reach of the finger in an unanesthetized patient.

If cystectomy has been decided on as the treatment of choice, the patient is prepared for removal of the bladder after provision has been made for diversion of the urinary stream by a method suited to his needs. He is prepared

with sulfonamide drugs, and blood for transfusion is ready at the time of operation. The rectal tube is inserted, a step which is important if ureterointestinal anastomosis has been performed previously, because a distended rectum is easily injured. Spinal anesthesia by the continuous method of administration is used; Graves and Thomson consider this technic invaluable. An extensive suprapubic incision is made and extended downward over the symphysis pubis far enough to insure adequate exposure. As the first step in the actual cystectomy, the peritoneum is dissected from the dome of the bladder except in cases in which the tumor occupies the peritonealized portion of the organ; in these cases the adjacent peritoneum should be removed with the specimen. As the dissection proceeds downward, further vascular attachments are divided until the lateral separation of the bladder is complete to the region of the vesical neck. The last blood vessels to be divided are found posteriorly beneath the bladder and lateral to the rectum on each side. Drainage is employed, and the drains are removed from seven to fourteen days after the operation.

Scholl¹⁸ reported a case of xanthoma and carcinoma in a diverticulum of the urinary bladder. Xanthomas are yellowish, benign, flat growths, considered by some authors to be neoplasms and by others to be connective tissue reactions following the collection of cholesterol esters of the cells of the affected site. Xanthomas most commonly occur in the skin but occasionally are found in the internal organs and only rarely in the urinary bladder. The patient, a man aged 59 years, complained of long-continued hematuria. Cystoscopic examination revealed the opening of a diverticulum in the base of the bladder, just above the left ureteral orifice. The blood was seen welling up from the opening. The most striking condition in the bladder was a grayish white, tumor-like mass which extended from the diverticular opening onto the floor of the bladder. With the patient under spinal anesthesia, the bladder was opened. The diverticulum was dissected out, and a segment of the vesical wall containing the sac and the grayish white region was resected. A large papillary carcinoma was found on the anterior surface of the diverticulum. Microscopic examination of the yellowish plaque revealed xanthoma, and examination of the larger papillomatous growth revealed a typical papillary carcinoma of a moderate degree of malignancy. The

18. Scholl, A. J.: Xanthoma and Carcinoma in a Diverticulum of the Urinary Bladder, *J. Urol.* 52:305-308 (Oct.) 1944.

wound healed readily, and two years later there was no recurrence of the lesion.

Deming and Lindskog¹⁹ reported a case of papillomatosis of the bladder. There was metastatic involvement of the entire urethra; subsequently metastasis occurred in the right lung. The metastatic lesions of the urethra and the lung were treated successfully by excision of the penile urethra and pneumonectomy. Although at the time of writing the primary lesion has been fully under control for thirteen years, metastasis has occurred in the right ilium, and other metastatic lesions of bone probably will develop. The histologic classification of papillomas of the bladder gives no opportunity for optimism in regard to their inherent tendency to metastasize. The justification of eradication of a solitary distant metastatic lesion is relief of symptoms and prolongation of life.

Congenital Obstruction of the Vesical Neck.—Pace²⁰ stated that congenital obstruction of the vesical neck may be present in infants and children who have a chronic or recurrent infection of the urinary tract. Frequency of micturition, straining, urinary incontinence and enuresis are suggestive symptoms of obstruction of the vesical neck. Coincidental anomalies of the upper part of the urinary tract may exist. Congenital obstruction of the vesical neck will damage the renal parenchyma if allowed to persist. The obstructing tissue may be removed transurethrally with little risk to the patient and with most gratifying results.

PROSTATE GLAND

Carcinoma.—Young²¹ stated that statistics show that carcinoma of the prostate occurs in at least 14 per cent of all men past 44 years of age. It is three times as common in men as carcinoma of any other internal organ.

In half of the cases carcinoma of the prostate is associated with prostatic hypertrophy. The two lesions are distinct in origin. Hypertrophy begins in the lateral and median lobes immediately adjacent to the urethra and rarely involves the posterior lobe, whereas carcinoma

begins in the posterior lobe in a large percentage of the cases and is easily palpable by rectum.

The medical literature in recent years has been filled with a long series of cases in which patients with prostatic disease have been treated by transurethral resection, but there is not a single report of an attempt to cure carcinoma by the radical operation. In nearly 50 per cent of Young's cases the patients were cured by his radical operation.

Young noted that several surgeons in the United States and abroad have tried to simplify his operation. Merely to remove the prostate with its capsule and the seminal vesicles without the anterior layer of Denonvilliers' fascia is not sufficient. Efforts to make the operation easier and less radical and to preserve a portion of the apex of the prostate, as was done by Belt, or to preserve the internal sphincter and muscle of the trigone, as was done by Geraghty, rob the operation of much of its radical character.

In a series of 184 cases there have been twelve deaths. All but 1 of these deaths occurred in cases in which Young did the operation, but a fair analysis shows that most of these occurred in the early days of the operation, when he was endeavoring to make the technic more and more radical in an effort to cure some patients who had deep-seated carcinoma. There has been one series of 54 cases without a death.

By the present technic of closure of the wound, normal micturition and complete urinary control have been obtained in almost every case.

Even in those cases in which there has been a local recurrence or bony metastasis at some period after Young's radical operation, there has been only 1 case in which obstruction to micturition was due to recurrence. Stricture has developed in a few cases, but this has been relieved by passage of filiforms and followers.

In order to show the type of case in which the radical operation will effect a cure, Young has given the history of 38 patients followed from five to twenty-seven years. There was no evidence of recurrence or metastasis in any of these patients. Of the 38 patients 11 were 50 to 59 years old, 20 were 60 to 69 years old, 5 were 70 to 79 years old and 2 were 80 to 82 years old. The oldest patient was 82 years of age and the youngest 51 years.

A careful inquiry as to even the slightest impairment of urinary control, such as escape of a few drops of urine on occasional coughing or sneezing or sudden movement or at the end of micturition, revealed that incontinence during both day and night occurred in only 1 case. In 2 cases the patients had almost complete incontinence.

19. Deming, C. L., and Lindskog, G. E.: Papillomatosis of Bladder and Entire Urethra; Infiltrating Cancer of Bladder; Late Pulmonary Metastasis; Successful Pneumonectomy, *J. Urol.* 52:309-318 (Oct.) 1944.

20. Pace, J. M.: Congenital Bladder Neck Obstruction, *Texas State J. Med.* 40:322-327 (Oct.) 1944.

21. Young, H. H.: The Cure of Cancer of the Prostate by Radical Perineal Prostatectomy (Prostate-Seminal Vesiclectomy): History, Literature and Statistics of Young's Operation, *J. Urol.* 53:188-256 (Jan.) 1945.

inence during the day but complete control at night. In 8 cases the patients had perfect control at night, and during the day there was only occasional escape of a few drops of urine, generally on sudden movement or coughing. Many patients did not even wear a pad, and not one found it necessary to use a urinal. All of the 11 patients were operated on a number of years ago. Twenty-seven of the cured patients had perfect urinary control, night and day, with not even leakage of a few drops. Not one had to wear a pad, and for practically every patient the urinary interval and stream were normal.

Colston²² considered the surgical removal of the prostate gland for carcinoma. From 1904, when Young first performed his radical operation, until 1939, radical operations were carried out on 88 patients in the Brady Urological Institute of the Johns Hopkins Hospital. One case has been excluded because the prostate was found to be the site of an extensive tuberculous disease, which was mistaken clinically for carcinoma. Of the 87 patients operated on for early carcinoma 5 died in the hospital, a mortality of 5.8 per cent. Critics of the radical operation have particularly emphasized the high mortality which occurs as a result of this operation, but certainly this mortality rate compares favorably with that of complete extirpation of malignant disease in other regions of the body.

Of the 81 patients who survived the operation (which was performed, it must be remembered, at varying times between 1904 and 1939) 39 (48.2 per cent) lived five years or more without evidence of recurrence and/or metastasis, 1 (1.2 per cent) was living at the time of writing but had roentgenographic evidence of metastasis, 29 (35.8 per cent) died within five years with recurrence and/or metastasis and 12 (14.8 per cent) died of intercurrent disease within five years with no evidence of recurrence and/or metastasis. If the last group is disregarded, the five year survival rate without evidence of recurrence and/or metastasis is 56.5 per cent.

For the 22 living patients without recurrence and/or metastasis the period of survival after operation is as follows: five years for 6 patients, six years for 7, seven years for 2, eight years for 1, nine years for 2, ten years for 1, eleven years for 1, twelve years for 1 and fourteen years for 1. Seventeen patients died of intercurrent disease without evidence of recurrence and/or metastasis after living five years or more after operation.

22. Colston, J. A. C.: Surgical Removal of Cancer of the Prostate Gland: The Radical Operation, *J. A. M. A.* **127**:69-72 (Jan. 13) 1945.

It has been the custom in Young's clinic for the examining physician to record his impression of the possibility of cure by radical operation in all cases of carcinoma of the prostate, and the operating surgeon similarly gives his impression of the prognosis in the operative note. With this information at hand, it has been possible to divide the 81 cases into two groups, one comprising 61 in which the prognosis was good and the other comprising 20 in which it was poor. Of the patients who had a good prognosis 19 (31.1 per cent) are living without evidence of recurrence and/or metastasis, from five to fourteen years after the operation, and 1 (1.6 per cent) is living but has roentgenologic evidence of metastasis to the humerus. Fifteen (24.6 per cent) have died of intercurrent disease without recurrence and/or metastasis from five to twenty-seven years after the operation, 9 (14.8 per cent) have died of intercurrent disease without recurrence and/or metastasis within five years after the operation and 17 (27.9 per cent) have died of recurrence and/or metastasis from a few months to fourteen years after the operation.

Of the 20 patients on whom the radical operation was undertaken with a poor prognosis for ultimate cure, 3 (15 per cent) are alive without evidence of recurrence and/or metastasis five, six and seven years respectively after the operation.

Bumpus, Massey and Nation²³ stated that the results of orchiectomy on 25 patients with carcinoma of the prostate confirm the impression that temporary relief accrues to almost all patients. Forty per cent of the patients who have been observed for a year or more after orchiectomy have had recurrence of symptoms. It is to be anticipated that a relapse eventually will occur in all the patients. It therefore remains to regulate better the use of orchiectomy and estrogens. These means of therapy probably should not be used until symptoms of an advanced malignant condition are manifest, and then they should be used separately and in succession rather than in conjunction.

Alvey²⁴ noted that regression of the local and metastatic growth of carcinoma of the prostate after castration or endocrine therapy occurs in the majority of cases. Immediate clinical improvement is observed in most cases. Questions of interest now are: How long will the im-

23. Bumpus, H. C., Jr.; Massey, B. D., and Nation, E. F.: Experience with Orchiectomy for Carcinoma of the Prostate, *J. A. M. A.* **127**:67-68 (Jan. 13) 1945.

24. Alvey, E. P.: Early or Late Orchiectomy for Carcinoma of the Prostate, *J. Urol.* **53**:143-153 (Jan.) 1945.

provement last? Will life expectancy be prolonged? Which is preferable as primary therapy, use of diethylstilbestrol or castration? Will early orchiectomy prevent or retard metastasis?

In 105 of the 110 cases reported by Alyea more than six months had elapsed since orchiectomy. In 25 per cent of the 105 cases the patients died within two years after the operation. In 40 cases two or three years had elapsed since the operation. Of the 40 patients, 32 per cent died within two years after operation. Metastatic lesions were present in 23 of the 40 cases. In 32 per cent of the 23 cases the patients died within one year after the operation; in 41 per cent the patients died within two years. Pain caused by metastatic lesions was present in 36 cases. In 41 per cent of these cases the pain recurred within one year after operation. In only 3 of 83 cases did obstruction recur after primary regression. In 26 cases in which there was no evidence of metastasis at the time of operation there was no evidence of metastasis for one year after operation. The author said that treatment should consist of orchiectomy and postoperative administration of small doses of diethylstilbestrol.

Emmett and Greene²⁵ stated that one indication for bilateral orchiectomy is carcinoma of the prostate with metastasis. Bilateral orchiectomy is especially efficacious when the metastatic growths have given rise to symptoms. The period of relief following orchiectomy varies from months to years. Whether any patients will remain permanently relieved seems extremely doubtful. Apparently, the large majority of patients have a recurrence of symptoms within a year. Whether or not "prophylactic" orchiectomy (done in the early stages of the disease, before metastasis has appeared) measurably influences the course of the disease is not yet known. This problem cannot be settled until more time has elapsed and a larger series of cases in which "prophylactic" orchiectomy has been performed has been studied. Pending the settlement of this problem, Emmett and Greene's present practice is to advise orchiectomy primarily for patients with metastasis, for relief of metastatic symptoms. Results up to the time of writing suggest that when orchiectomy is performed in conjunction with transurethral resection the frequency of recurrent obstructive symptoms requiring subsequent prostatic resection is reduced; furthermore, if such symptoms do ap-

pear, the interval of time between resections is increased. Treatment with estrogens after transurethral resection is also being given to a group of patients who do not show evidence of metastasis, to see whether the course of the disease can be appreciably altered over a substantial period. Emmett and Greene are interested in knowing whether preliminary estrogenic therapy in such cases will tend to nullify the palliative effects of castration if the latter procedure should become necessary for control of symptoms later on.

Rathbun²⁶ stated that orchiectomy for carcinoma of the prostate has been performed in his clinic on 23 patients during the last three years. With 2 exceptions it has been done as an adjunct to other procedures. Two patients who had extensive metastatic lesions of bone were not benefited in any way and died. In 1 case in which there was extensive metastasis the pains lessened for three months but recurred. One case was too recent to permit comment. In all the remaining 19 cases improvement varying from moderate to what might be called dramatic, for periods ranging from four months to three years, was shown.

In only 2 cases was orchiectomy the only form of treatment. Both of the patients, 1 two and a half years postoperatively and 1 one year postoperatively, are still living and comfortable and have practically no obstructive symptoms.

In 2 cases in which the lesion was thought to be suitable for a radical perineal operation, the operation was undertaken but was abandoned because the lesion was found more extensive than had been anticipated. A partial prostatectomy was performed; this was supplemented by castration and use of radon seeds. The patients are reasonably comfortable two years postoperatively but have obvious carcinoma, as evidenced by rectal palpation.

In 2 cases in which the diagnosis had not been definitely established, suprapubic prostatectomy was undertaken. In 3 other cases a two stage suprapubic prostatectomy was performed and the diagnosis of carcinoma was not made until the report of the pathologist was received. In 2 cases a temporary cystotomy was followed by castration and use of radon. In all cases in which a suprapubic incision was made, the wounds closed in from three to six weeks. In 4 cases transurethral resection was followed by castration and use of radon, and in 3 cases transurethral resection was followed

25. Emmett, J. L., and Greene, L. F.: Bilateral Orchiectomy for Carcinoma of the Prostate Gland: Clinical Experience, *J. A. M. A.* 127:63-67 (Jan. 13) 1945.

26. Rathbun, N. P.: Orchiectomy for Carcinoma of the Prostate: Personal Experiences, *J. Urol.* 52:325-329 (Oct.) 1944.

ly castration. In only 1 case has Rathbun noted any regression of bony metastasis.

All 19 patients are at present fairly comfortable. Three patients have about 120 cc. of residual urine. The remainder have 50 cc. or less, and 2 patients are able to empty their bladders completely. With 1 exception all the patients show evidence of residual carcinoma on rectal palpation. One patient has no evidence of the disease and is practically free of symptoms two and one-half years after operation.

While Rathbun is convinced that orchiectomy will not cure carcinoma of the prostate, he believes that it is a valuable addition to treatment, especially when combined with other methods and particularly when combined with the local application of radium.

Herbst²⁷ stated that chemical treatment will not cure carcinoma of the prostate. If the original growth can be completely removed, operation is the procedure of choice. The chemical treatment should comprise (1) removal of the secreting tissue of the testes, (2) introduction of a group of chemical substances by one of three means—orally, by hypodermic injection or by implantation of pellets—(3) a combination of the two preceding methods, (4) nutritional measures and (5) administration of vitamins.

The chemical substances employed consist of estradiol dipropionate, diethylstilbestrol, ethinyl estradiol and pellets of estradiol benzoate. Apparently, all these substances produce the same effect.

The practical objective of chemical treatment of carcinoma is modification of the soil in which the malignant cells grow, in order to inhibit their growth.

Dietary measures consist of a high calory, high vitamin, low cholesterol nutritional intake. The purpose of the high calory, high vitamin diet is to improve the general health of the patient and to increase his resistance.

There is no way of determining what the nature of response of a patient will be. The dose of the substance used should be the smallest possible amount that will accomplish satisfactory control. In many cases in which castration has ceased to be effective additional control may be accomplished by subsequent administration of the aforementioned chemical substances. The procedure which will in most instances insure the most rapid favorable effect on the carcinoma is castration. The plan for the most prolonged satisfactory control of the malignant process

consists of castration and subsequent administration of the aforementioned chemical substances in as small doses as possible. Herbst concluded that the chemical treatment of carcinoma of the prostate renders available a relatively simple method for relief of pain and satisfactory inhibition of the malignant process for various periods.

Cifuentes²⁸ reported his experience with the use of synthetic follicular substance (diethylstilbestrol) in 10 cases of carcinoma of the prostate in which the clinical symptoms were so evident that there could be no doubt about the diagnosis. The stony hardness of the prostate was characteristic. In all the cases he refrained from using castration, in order to observe with more certainty the effects of the follicular treatment. Four of the cases were discussed in some detail; in the remaining 6 the patients still are undergoing treatment. However, 5 of the 6 patients already have shown signs of improvement.

In the 4 cases reported in detail, the patients were all suffering from dysuria and pollakiuria night and day. These were followed by more or less complete urinary retention, anemia, loss of appetite and general debility. One of the patients had been operated on five months previously, and a bilobular adenoma weighing 30 Gm., with nuclei of carcinomatous degeneration, had been removed. The tumor recurred five months later. The 4 patients received 3 mg. of diethylstilbestrol subcutaneously each day until a total of 60, 69, 120 and 60 mg. respectively had been given, in twenty, twenty-three, forty and twenty days respectively. After the fourth or fifth injection, the pains began to diminish, spontaneous urination occurred, appetite returned and the general condition showed great improvement. In 1 case, in which the patient still is undergoing treatment, all pain has disappeared and the prostate is softer, although still of somewhat fibrous consistency. This patient is being observed with great interest.

In all the author's cases, as in most cases reported in the literature, an indisputable improvement has been observed under the treatment, an improvement that could, in fact, be called almost spectacular in certain cases. The prostate grows softer, and the urinary symptoms have been completely relieved. Some authors have even reported disappearance of metastatic lesions.

It is not known whether these results will prove permanent. The author's view is that

27. Herbst, W. P.: The Effects of Biochemical Therapeutics in Carcinoma of the Prostate: Further Observations. *J. A. M. A.* 127:57-59 (Jan. 13) 1945.

28. Cifuentes, P.: The Modern Treatment of Cancer of the Prostate with Synthetic Follicular Hormones. *Arch. españ. de urol.* 1:11-19 (July) 1944.

treatment should be continued with gradual decrease of dosage, even after considerable improvement occurs. Like all new methods, this one requires long and continuous observation before its value can be determined.

Stirling²⁹ reported a series of 40 cases of carcinoma of the prostate in which resection, castration or estrogen therapy was utilized. Of the 40 patients 57 per cent survived for an average of sixteen months.

Shrinkage of the malignant lesion and relief of pain were observed early and usually lasted until the patient died. Castration and estrogen therapy seem to produce palliative relief; neither prevents recurrence nor retards metastasis. Resection should be utilized if partial or complete obstruction of micturition is encountered. Serum acid phosphatase levels were generally within normal limits in 21 instances and afforded little additional aid in the diagnosis of the disease unless metastasis was in evidence. High blood acid phosphatase levels are an indication of osseous metastasis. Negative observations are of little diagnostic value. Estrogen therapy is indicated in cases in which the patients refuse castration or as a supplement to orchiectomy. It is also valuable in controlling hot flashes. These observations seem to indicate that neither of these procedures, alone, will completely eliminate androgen activity and that they should supplement each other.

Moore, Wattenberg and Rose³⁰ discussed the mammary changes caused by administration of diethylstilbestrol in the treatment of carcinoma of the prostate gland. In sections of an adult male breast obtained before treatment with diethylstilbestrol, the interstitial tissue is scarce, and there is an occasional duct in the thin, fibrous stroma, with a few small blood vessels. The epithelial cells of the ducts for the most part consist of a single layer and have a thin basement membrane. The epithelial cells are usually large and pale and have large nuclei. After the patient has been treated with diethylstilbestrol, the breast becomes enlarged and often painful. Then, sections are obtained at intervals during treatment, some progressive changes take place. During these progressive changes there is proliferation of the epithelium of the ducts. The walls of the ducts increase in thickness from one to ten or more times. Also the ducts become

elongated. Early in the course of these changes one can find budding of the ducts. At ten or more buds can be found developing on a duct which was present before treatment. There is also increase in vascularity through the connective tissue. The epithelium of the ducts along with its proliferations contains large cells of various shapes and sizes. The cells are multiplied to such an extent as to occlude the duct. The cells stain deeply, and the basement membrane remains intact and is not invaded. In none of the ducts can one find secretory cells; there is any secretory process taking place.

Tissue removed from prostatic carcinoma after transurethral resection before treatment with diethylstilbestrol showed that most of the ducts were arranged in acini and that some formed solid nests or cords. The cytoplasm appeared swollen and foamy. The nuclei were round and were situated in the central portion of the cells. Many of the cells contained large round vacuoles.

After treatment with diethylstilbestrol, the carcinomatous tissue showed regression of the cytoplasm; a large percentage of the nuclei stained deeply, were pyknotic and were small and irregular in shape. The pyknotic nuclei were scattered and had no definite arrangement. In some spaces no nuclei could be found. The nuclear diameter had been reduced nearly 50 per cent in most sections. In the center of many acini, pyknotic nuclei and remnants of cell membranes could be found crowded together without attachment to the periphery of the acini.

The mammary changes which have been found are not serious but are dangerous in that the patient often stops taking diethylstilbestrol when pain in the breasts begins or when it becomes severe.

Gross enlargement of the breasts, as well as microscopic proliferation, is no indication of the amount of benefit the patient is receiving. Many patients have little pain in the breasts and only slight microscopic changes, but the prostate gland, which is carcinomatous, is reduced greatly in size. The patients also are relieved of their pain and gain weight. In other patients there are gross enlargement of the breasts, indicative of chronic cystic mastitis, and well defined hyperplasia, with little change in the prostatic carcinoma; in yet others the pain is not relieved, and they do not regain the lost weight. The authors reserve orchiectomy for those not benefited by endocrine therapy.

The authors have not observed any malignant changes in the breasts from diethylstilbestrol and rather doubt if such changes ever will be found. One difficulty is uncertainty as to the correct

29. Stirling, W. C.: An Analysis of Forty Cases of Carcinoma of the Prostate, *J. Urol.* 53:154-159 (Jan.)

30. Moore, G. F.; Wattenberg, C. A., and Rose, H.: Breast Changes Due to Diethylstilbestrol During Treatment of Cancer of the Prostate Gland, *J. A. M. A.* 127:60-62 (Jan. 13) 1945.

lose of diethylstilbestrol for treating carcinoma of the prostate. The authors have given as much as 60 to 80 mg. per day, but how much of it is excess or waste is not known.

Herger and Sauer³¹ reported on androgen control therapy in 130 cases of carcinoma of the prostate. Seventy-nine of the patients were followed for from one to two and a half years. Twenty-seven of the remaining 51 patients were followed for from four to twelve months, and twenty-four died of the disease within the first year after treatment was begun.

In 107 cases the diagnosis was made by biopsy. In the remaining 23 cases, the diagnosis was based on the observations on rectal examination, which revealed far advanced infiltrating carcinoma of the prostate.

Metastasis was present in 65 of the 130 cases. The sites of the metastatic lesions were as follows: bone in 59 cases, distant lymph nodes in 5 cases and a lung in 1 case.

Herger and Sauer employed castration alone or in combination with diethylstilbestrol medication preferably in cases in which there was demonstrable metastasis or in cases in which the disease was progressing rapidly. In contrast, treatment with diethylstilbestrol, usually in doses of 1 mg. daily, was reserved for patients with apparently low grade malignant tumors with no demonstrable metastasis, in whom little progression of the lesion was anticipated. Diethylstilbestrol alone was used in cases of moderately advanced lesions in which the symptoms were mild or absent, in cases in which the patients refused castration and in cases in which the patients' conditions, for various reasons, made orchiectomy unsuitable.

Orchiectomy alone was employed in 26 cases. In 19 of these cases metastasis had occurred. In 48 other cases castration was either preceded or followed by administration of diethylstilbestrol; in 35 of these cases metastatic lesions were present. In the remaining 56 cases the patients were treated with diethylstilbestrol only. Metastasis was present in 11 of the 56 cases.

In 17 of the series of 130 cases the response to treatment was so favorable that clinical improvement coincided either with apparent temporary arrest or with regression of the disease. Remarkable improvement in the roentgenologic appearance of the metastatic lesions of bone was noticeable in 2 of the 3 cases in which bone was involved. In both cases orchiectomy had been performed more than two years previously.

31. Herger, C. C., and Sauer, H. R.: Androgen Control Therapy in One Hundred and Thirty Cases of Carcinoma of the Prostate, *Surg., Gynec. & Obst.* 80:128-138 (Feb.) 1945.

Clinical improvement, in spite of evidence of progressing disease, occurred in 20 cases.

Of the patients with metastasis, 83.1 per cent showed clinical improvement during the first four months of treatment, but this percentage dropped to 75 between the fourth and seventh months, to 58.3 between the eighth and twelfth months and to 11.1 at the end of two years. It is apparent that in cases in which metastasis is present a pronounced decline in the percentage of patients who are benefited occurs at the end of the first and at the beginning of the second year.

For 11 of 56 patients who were treated with diethylstilbestrol alone delayed failures occurred, as compared with 27 in the group of 74 castrated patients.

Data on the effect of treatment on the primary lesion were available for study in 116 of 130 cases.

While increase in size of the prostate developed in only 4.3 per cent of the patients during the first four months of treatment, such increase was found in 21.1 per cent of the patients between eight and twelve months, in 50 per cent between nineteen and twenty-four months and in 56 per cent between twenty-five and thirty months.

In contrast, the number of patients who responded with regression in size of the prostate or softening in consistency, or both, declined after a period of one and a half years. Herger and Sauer's results revealed that a favorable response was maintained at a level of about 60 per cent of the patients during the first eighteen months of treatment.

Sufficient data on the response to treatment of symptoms caused by obstruction were available for study in 105 of the 130 cases. Forty-two of the 105 patients had either no residual urine or less than 50 cc. during the time of observation. Twenty-six patients had complete retention at the time of admission to the hospital. In 14 of them retention persisted; 6 were relieved temporarily, and 6 obtained relief which continued up to the time of writing. Thirty-seven patients had varying amounts of residual urine, accompanied with dysuria, urinary frequency and difficult micturition. Improvement of obstructive symptoms coinciding with a tendency to decrease of residual urine was observed in 23 patients, but in 5 of them improvement was only temporary. In the remaining 14 patients the amount of residual urine increased in spite of treatment: in 4 of these complete retention developed during the treatment, necessitating transurethral resection, cystostomy or drainage with indwelling catheter. From these figures it appears that up to the time

of writing a continued favorable response to treatment was obtained from only 24 of 63 patients in whom symptoms of obstruction were present.

In 48 cases the effect of treatment on the metastatic lesions in bone was unsatisfactory as a rule; no noticeable changes in the appearance of the bone lesions in the roentgenogram were observed in 13 cases. Further progression of previously demonstrable metastatic lesions or metastatic spread to other parts of the skeleton occurred in 25 cases. In 6 others bony metastasis developed in spite of treatment.

Improvement in the roentgenologic appearance of metastatic bone lesions was demonstrable in only 4 cases, but improvement was not sustained in 2.

Herger and Sauer's studies on the effect of androgen control treatment of prostatic cancer indicated that favorable response to this method of treatment was accomplished in numerous instances. However, during prolonged observation it became evident that in a considerable number of cases in which initial improvement was manifest failure later ensued. In the treatment of patients with far advanced or metastatic disease androgen control treatment has proved its value as a method of prolonging life.

Palomo³² stated that carcinoma of the prostate is of two types. In more than 75 per cent of the cases the disease begins in the posterior lobe. In the remaining cases the disease begins as an adenomatous hypertrophy and the presence of carcinoma is not suspected until it is revealed by microscopic examination. A morphologic peculiarity is the diversity of types of carcinoma of the prostate. Adenocarcinoma is the commonest type, but scirrhous, medullary and squamous cell carcinoma may be found, sometimes in the same specimen.

Carcinoma of the prostate not infrequently occurs in men who are younger than those who usually have benign hypertrophy. Of 276 patients, the youngest was 45 years old and 4 others were less than 50 years of age. The greatest incidence (42 per cent) was in men in their sixth decade.

The symptoms of carcinoma of the prostate occur late and are not easily distinguished from those of adenomatous hypertrophy. More than 50 per cent of the patients had had symptoms less than one year. Urinary disturbances, usually the first symptoms, were present in all but 12 of the patients. Pain, which often is due to skeletal metastasis, was present in 63 patients, hematuria in 61 and loss of weight in 34. These

are all late manifestations and do not help in early diagnosis of the condition. Four patients with extensive carcinoma had no symptoms whatsoever, and the tumors were discovered during physical examination for other purposes.

The prognosis of carcinoma of the prostate is grave. In cases in which the tumor has not extended beyond the prostate and its capsule, radical removal of the prostate and seminal vesicles plus castration would seem to offer the best hope of a cure.

From 1921 to 1938, a period of seventeen years, various forms of treatment were utilized, for the most part open operation and implantation of radon seeds, often with supplementary deep roentgen therapy. Eighteen of the 165 patients who were treated in this period are known to have lived three years or longer.

From January 1938 to January 1941, 111 patients were treated. Sixty-four were treated without castration, and 47 were treated with castration. Of the former group, 44 patients who underwent prostatectomy or resection were followed. Thirteen of these lived three years or longer, all after open operations. Of the 47 patients who were castrated, 20 were alive on Jan. 1, 1941, 8 after open operation and castration, 16 after transurethral resection and castration and 1 after castration only.

The castrated patients show a prompt and often complete freedom from pain; they gain weight and have a feeling and appearance of well-being.

Nesbit³³ said that there is no doubt that castration or administration of estrogen results in suppression of carcinogenic activity in most cases but that substantial evidence is still lacking to show the ultimate value of this treatment or, in fact, to point out clearly whether early employment of endocrine therapy is of greater ultimate value to the patient than delayed treatment.

Both Alyea and Stirling have reported that the majority of patients treated for advanced carcinoma of the prostate gland have been significantly improved by castration, and the evidence in each series seems to indicate that the lives of the patients so treated have been not only prolonged but also made more comfortable. It is also evident that remission of symptoms is in some way related to a suppression of carcinogenic activity, although in some instance metastasis, when present, has advanced during the period of symptomatic remission.

In the series studied at the University of Michigan Hospital, there were 32 patients who

32. Palomo, A.: Carcinoma of the Prostate Gland, *J. Urol.* 53:166-187 (Jan.) 1945.

33. Nesbit, R., in discussion on Waltenberg and Ross, Alyea²⁴ and Stirling,²⁹ *J. Urol.* 53:161-162 (Jan.) 1945.

at the time of castration showed no evidence of distant metastasis or extensive local involvement but who at the time of the second follow-up report showed symptoms and signs of advanced disease and metastasis had developed in 31 per cent of the group while 12.5 per cent had died of cancer. Emmett reported a series of 220 cases of carcinoma in which orchiectomy was performed. In 52 of the cases there was no evidence of metastasis when the patients were castrated. Emmett reported that now 35 per cent of the patients have shown signs of metastasis and 15 per cent are dead.

In view of these reports, the observations of Alyea are of significant importance. He has reported that 26 of his patients who had no evidence of metastasis at the time of castration have been followed carefully by him and that none of these patients have shown any evidence of extension of the primary tumor or of metastasis.

Cummings³⁴ said that there is a trend to utilize castration in cases of advanced carcinoma in which symptoms of metastasis are present. It is in this type of case that the subjective response is brilliant. Pain was relieved immediately after bilateral orchiectomy in 88 per cent of Cummings' series of cases in which that symptom was present prior to castration. This percentage is somewhat higher than that in the reports under discussion. The objective changes following institution of endocrine therapy in cases of advanced carcinoma are likewise often brilliant. Definite regressive changes in the primary neoplasm occurred in 32 per cent of Emmett's cases and in 34 per cent of the cases reported by Nesbit and Cummings. Some degree of regression in size of the prostate was thought to have occurred in 66 per cent of Cummings' cases. Seventy-one per cent of Emmett's patients experienced definite improvement of urinary function after bilateral orchiectomy alone. In Cummings' series of cases, 9 of 14 patients who had no operation for the relief of prostatic obstruction experienced improvement in micturition following castration. In the group of patients with metastases, 78 per cent of Emmett's and 84 per cent of Cummings' patients survived the nine month period shown by Bumpus in a similar group of patients for whom endocrine therapy was not used to be associated with only 33 per cent survival. These illustrative comparisons seem to demonstrate the efficacy of castration when prostatic car-

cinoma has metastasized. This therapeutic procedure has been followed by an average remission of carcinogenic activity for eleven and four-tenths months in cases in which symptoms return. The fact that metastasis occurred in 35 per cent of Emmett's patients but was not detected prior to castration and the fact that 15 per cent of the patients died suggest that this procedure does not constitute prophylaxis against extension of this neoplasm. In Cummings' experience, metastasis occurred in 18.8 per cent of cases and 12.5 per cent of the patients died not less than twenty-one months after bilateral orchiectomy.

Colston³⁵ said that the mortality associated with radical operation for carcinoma of the prostate has been greatly exaggerated. A recent study of all patients subjected to this procedure from 1904 until 1939 at the Brady Urological Institute of Johns Hopkins Hospital shows a hospital mortality rate of 5.8 per cent.

Since Jan. 1, 1945 Colston has seen 4 patients with fairly extensive disease of the whole prostate gland but without evident extension beyond the capsule. For all of these patients it would have been technically possible to carry out the radical operation, but the prognosis for cure by this procedure would not have been good. These patients were given diethylstilbestrol in 1 mg. doses daily for approximately two months. In each case there was a regression of the neoplasm, as determined by rectal examination. The radical operation eventually could be performed on each patient without difficulty. At operation the seminal vesicles were found to be soft and uninvolved and could be easily removed en masse with the prostate in its capsule.

Colston believes that endocrine therapy will open new possibilities in the treatment of carcinoma of the prostate in that it may be possible to cause regression of the neoplasm in some cases in which the lesion might be considered inoperable when the patients are first seen and that it may be possible to perform a radical operation after a course of this treatment. Patients in whom the disease is too extensive for radical extirpation should be given estrogenic therapy in the hope that the growth will regress sufficiently to permit complete removal of the involved prostate. Orchiectomy should be reserved for the control of pain and metastasis, in other words, as the last resort, or better, perhaps, the last two resorts.

In a recent study of 81 patients subjected to the radical operation at the Brady Urological Institute prior to 1939, it was found that in

34. Cummings, R. H., in discussion on papers of Herbst,²⁷ Moore and others,³⁰ Emmett and Greene,²⁵ Bumpus and others²³ and Colston,²² J. A. M. A. **127**: 72-73 (Jan. 13) 1945.

35. Colston, J. A. C., in discussion on Young,²¹ pp. 253-255.

only 4 patients did recurrence of urinary obstruction take place. In 2 patients the condition was easily handled by simple urethral dilation, and in only 1 patient was transurethral resection necessary.

Carcinoma of the prostate can be recognized in its early stages. In doubtful cases performance of biopsy can render the diagnosis certain. In cases of early carcinoma the whole gland in its capsule, with the neoplasm, can be removed. The radical operation presents no difficulties to any one with experience in perineal surgery, and the operative mortality is certainly not prohibitive. In the future more and more radical prostatectomies should be done.

Kearns³⁶ said that in general the salutary effects of castration and of estrogens in cases of carcinoma of the prostate are less enduring than had been hoped for previously. Evidence points to the generalization that if one method fails the other method used alone or in combination also will fail. Castration was not employed in any of the 78 cases in Kearns's series. Simple estrogenic treatment will gain in favor because all of the attainable benefits of castration minus some of its undesirable side effects are obtainable by judicious use of the true hormone estradiol, given to each patient by the most effective route. The changes produced by estrogens, which abruptly alter the blood picture and the clinical course of the disease, are unquestionable evidence of their profound influence. Of 42 private patients who have been followed, approximately 60 per cent were definitely benefited for periods exceeding six months. In 15 cases surgical intervention was indicated because of urinary obstruction. Through prompt application of estrogenic therapy, urinary antiseptics and use of continuous or intermittent catheterization, the 15 patients obtained improvement in general health, shrinkage of the prostate and ability to empty the bladder with little or no residual urine. Of these 15 patients 4 died, 2 of carcinoma and 2 of intercurrent disease. In no instance did significant urinary retention recur. The sedimentation rate of the erythrocytes as an aid in diagnosis and an indicator of the progress of the disease has proved helpful. Approximately 85 per cent of the patients will show a deviation from normal, and this fact gives the sedimentation rate a much wider range of usefulness than estimations of the concentration of serum phosphatase. Kearns's preference for nonsurgical treatment is based on several

considerations. From the standpoint of economy, the evidence is overwhelmingly in favor of the nonoperative treatment. The hospital expense for the average patient would purchase a supply of estradiol sufficient to last two years. The operative fee no doubt would purchase a number of added years' supply, carrying well beyond the life expectancy of men in this age group. In more than three years several of Kearns's carcinomatous patients were maintained in good health with small doses of estradiol, that is, 0.05 mg. twice daily, without need of increments. It is his impression that the usual dose may be ineffective but that when an adequate dose is established further increments are ineffective.

Alcock³⁷ mentioned a case of carcinoma of the prostate in which roentgenologic examination disclosed that metastatic lesions disappeared or became less evident after administration of diethylstilbestrol. Alcock is not optimistic in regard to the surgical treatment. A lesion to be amenable to surgical treatment must have certain characteristics. To be capable of elimination it must be so situated that one can remove a portion of healthy tissue around the lesion. The aim of all treatment of cancer should be just one thing, and that is cure. Either the patient is cured, or he is not cured. A patient who has a recurrence of carcinoma ten years after treatment is no more cured than the one who has a recurrence in six months. Alcock agrees that operation offers the only possibility of curing carcinoma of the prostate but said that operation is applicable in such an infinitely small percentage of cases that it cannot be the answer to the whole problem. He doubts that the surgical possibilities will be extended either by greater perfection of technic or by earlier diagnosis. No one has ever claimed that either orchiectomy or administration of diethylstilbestrol will cure carcinoma of the prostate.

Ballenger³⁸ said that if a reasonably high percentage of patients with early carcinoma of the prostate would consult urologists and if the urologists had the technical skill of Young in this type of work, the problem would not be a troublesome one. Other factors, however, must be considered; for instance, a patient with early carcinoma of the prostate might prefer complete perineal prostatectomy in order to gain a greater expectancy of life, in spite of the possibility of loss of urinary control or of a vesico

36. Kearns, W. M., in discussion on papers of Herbst,²⁷ Moore and others,³⁰ Emmett and Greene,²⁵ Bumpus and others²³ and Colston,²² *J. A. M. A.* 127:73 (Jan. 13) 1945.

37. Alcock, N. G., in discussion on papers of Herbst,²⁷ Moore and others,³⁰ Emmett and Greene,²⁵ Bumpus and others²³ and Colston,²² *J. A. M. A.* 127:73 (Jan. 13) 1945.

38. Ballenger, E. G., in discussion on Young,²¹ pp 255-256.

rectal fistula. Ballenger remarked that if he were the patient he might prefer the less radical procedure, of orchiectomy with transurethral removal of obstructing tissue at the vesical neck, in order to escape the possibility of loss of control of micturition or to prevent formation of a vesicorectal fistula.

Borjas³⁹ discussed the several available methods of removing obstruction of the vesical neck and considered the relative advantages and disadvantages of each. His attention was directed to the transvesical method of prostatectomy.

While Freyer's classic operation is easy to carry out and has been brought to a high degree of perfection, with excellent results in carefully selected cases, the fact remains that the surgeon works in the dark, so that grave hemorrhages are not infrequent and postoperative obstruction and fistulas are commonly observed. A long period of hospitalization is required, sometimes reaching four, five or eight weeks. These considerations led Borjas to adopt the method of Thomson Walker and the English school, that is, to perform the transvesical operation under direct vision. This method makes it possible to secure a clean and regular bladder wound, without the tags and flaps which under the old method remain to invite infection and necrosis, which impair cicatrization.

The urethral mucosa is separated with scissors and not by tearing off the adenomatous mass. This secures regulation of the bladder neck, of the walls of the prostatic cavity and of the end of the urethra and promotes correct cicatrization and better postoperative function. A large tampon is placed in the prostatic cavity, to prevent hemorrhage. Then the source of the hemorrhage, if there is one, is determined, and the bleeding is stopped. Nothing is more variable than the amount of bleeding observed after enucleation; in some cases there is none at all. If a considerable amount of hemorrhage does occur, it is necessary to stop it summarily, in order to prevent anemia, with possible fatal results. No permanent urethral catheter is at first inserted, but suprapubic drainage with a Pezzer catheter is used for one week, after which a permanent catheter brings about complete closure in fifteen to twenty days. Postoperative endoscopic inspection usually will reveal perfect cicatrization without obstruction at the end of thirty days.

Prostatic Operations.—Slotkin and Fletcher⁴⁰ said that pulmonary complications in old, debili-

tated patients who require prostatic operations are a common cause of death. Most of these patients do not have true pneumonia but have so-called wet chests, owing to capillary secretions. Ascorbic acid, which increases the tonicity of the capillaries, has been of great value in alleviating the symptoms and in restoring prompt pulmonary action by causing disappearance of the infiltration. Irrespective of the blood levels or the deficiency of vitamin C, ascorbic acid is a valuable adjunct in tiding these aged patients over their critical postoperative period.

TESTIS

Tumors.—Matassarini⁴¹ reported a case of embryonal adenocarcinoma of the testis in which the patient was an infant. He stated that teratoma of the testis is not a common tumor. The infrequency of its occurrence is evidenced by many previous statistical reports in medical literature. This tumor, which is uncommon in adults, is even rarer in infants. In a review of 5,500 cases of testicular tumors reported in full detail Gilbert found that only 131 of the patients were less than 15 years of age. In 42 of the 131 patients the tumor was a dermoid; in 89 it was a teratoma. In 17 of the 89 cases of teratoma the patients were 1 year of age or less.

Embryonal adenocarcinoma of the testis is usually unilateral and arises from the rete testis. It grows rapidly and is highly malignant, even though it does not attain large size. Pain and swelling are predominant symptoms in infants as well as in adults; swelling is usually the earlier of the two symptoms. Physical findings on examination are usually limited to enlargement of the testis.

In the differential diagnosis one should consider benign tumors, syphilis, tuberculosis, hydrocele and hematocele. It is interesting that 15 to 25 per cent of all malignant tumors of the testis are associated with a small hydrocele. Early diagnosis and treatment are necessary. Most authors agree that simple orchiectomy is the operation of choice. Preoperative irradiation may be employed, and all authors favor the use of postoperative irradiation.

Cryptorchism.—Jason⁴² said that cryptorchism is of two types: (1) incompletely de-

40. Slotkin, G. E., and Fletcher, R. S.: Ascorbic Acid in Pulmonary Complications Following Prostatic Surgery: A Preliminary Report, *J. Urol.* 52:566-569 (Dec.) 1944.

41. Matassarini, F. W.: Embryonal Adenocarcinoma of the Testicle in an Infant: Case Report, *J. Urol.* 52:575-577 (Dec.) 1944.

42. Jason, A. H.: Cryptorchidism, *Am. J. Surg.* 65:353-360 (Sept.) 1944.

39. Borjas, A.: The Surgical Problem of Bladder Neck Obstructions: Open Suprapubic Prostatectomy Under Direct Vision, *Rev. de urol.* 2:1-13, 1944.

scended testes and (2) ectopic testes. In cases of cryptorchism of the first type the testis may be arrested at any stage in its normal descent. Incomplete descent may be due to one or more of the following causes: hypopituitarism, producing, as the term denotes, insufficient anterior pituitary gonadotropic stimulation of the testis; primary hypogonadism, resulting in insufficient reaction to pituitary stimulation, and hypothyroidism, owing to failure of primary tissue differentiation and lack of testicular response.

The gratifying results of endocrine treatment of incompletely descended testes confirm the belief that testicular function is under the control of the endocrine system.

In contrast to this type of cryptorchism, the ectopic testis has a normal endocrine stimulus, but the descent is arrested by purely mechanical factors, and the anomaly is, therefore, not amenable to hormonal therapy. The displacement usually occurs after the organ has passed through the full length of the inguinal canal.

In addition to being of normal size, the ectopic testis, unlike the incompletely descended testis, is usually accompanied with indirect inguinal hernia. In children, cryptorchism may be apparent rather than real, for, owing to the spasticity of the cremaster muscle, the testis may be displaced in an upward direction and thus be temporarily missing from the scrotum.

Normally, until about the age of 13 years, little growth occurs in the testis so that before puberty the histologic appearance of scrotal and of undescended testis is similar. After puberty the ectopic testis may fail to generate a mature germinal epithelium because of the prevalent abnormal temperature outside the scrotum. In these circumstances a mechanical factor rather than an endocrine substance determines the condition of the testis. This distinction between endocrine and mechanical control is a vital factor in the treatment of cryptorchism. The abnormal anatomic conformations obviously preclude satisfactory effects from endocrine therapy.

The size of the testis is a fair index of its eventual reaction after it has been placed in its natural position in the scrotum. In a small, atrophic organ, the germinal cells probably disappear and no further development occurs, whereas in a testis of moderate size in a patient past puberty young germinal epithelium capable of producing mature spermia still survives and further development will occur.

The following substances are employed in attempts to cure cryptorchism: the anterior-pituitary-like substance which appears in the urine during pregnancy; extracts of the anterior

lobe of the pituitary body proper, and pregnant mares' serum.

Justification for orchidopexy is based on the following grounds: 1. When the testis is placed in the scrotum before puberty, it produces hormone and sperm. 2. A bilateral cryptorchid is sterile. 3. Statistical inquiries and studies have shown that malignant changes are twice as common in an undescended as in a normal testis. 4. An undescended testis is more liable to torsion, strangulation, chronic inflammation and trauma than a normal testis. 5. Epididymal involvement of the scrotal testis may leave the unilateral cryptorchid sterile. 6. The undescended testis may have a psychologic effect.

The surgical treatment of cryptorchism may be begun at any age but preferably should be instituted before puberty. However, it should not be discontinued because the patient is beyond this age. Operation should not be delayed in cases in which the patients have not reached the age of puberty. The sooner the cryptic testis is placed in the scrotum, either by endocrine or by surgical means, the greater the likelihood of serviceable spermatogenic function.

Lason concluded that in cases of incomplete descent of the testis surgical intervention is contraindicated except in conjunction with endocrine therapy. For ectopia of the testis operation is the treatment of choice, and endocrine therapy, obviously, is unnecessary. If it is uncertain in which category a misplaced testis belongs, a complete endocrine study should be made and correct endocrine therapy should be instituted. If there is apparent failure of response, surgical treatment is justified, even if the gland is impalpable. Anorchia is extremely rare.

Rupture of the Testis.—Counseller and Pratt⁴³ reported a case of rupture of the testis and reviewed the cases found in the literature. The patient, a boy aged 17 years, injured himself by colliding with another boy while running and received a blow in the region of the symphysis pubis. The scrotum enlarged to the size of an orange, and there was associated edema at the base of the penis. At operation, the scrotum was opened, and a large amount of blood extruded from the cavity of the tunica vaginalis. The testis was then delivered and found to have been ruptured and its upper pole injured. The rupture was compound, and almost a fourth of the testis was fragmented. The torn segments were removed and the testis sutured and replaced in

43. Counseller, V. S., and Pratt, J. H., Jr.: Rupture of the Testicle: Report of Cases and Review of Literature, *J. Urol.* 52:334-337 (Oct.) 1944

he scrotum. The postoperative course was uneventful.

Five other cases found in the literature were reviewed, and Counseller and Pratt drew the following conclusions: In spite of a severe injury to a sensitive organ, in only a third of the cases was the initial shock severe and half of the patients were able to continue strenuous physical activities. In all cases the treatment was surgical, and in only 1 could the testis be saved. The end result in their case will probably be atrophy of the testis, although more than half the testis was uninjured.

Traumatic Epididymitis and Orchitis.—Mason and Reifstein⁴⁴ reported a case in which epididymitis and orchitis followed trauma. The patient was 31 years of age. He had been struck in the left groin and thereafter he had had considerable pain and swelling in this area. On examination, the left scrotal contents were twice the usual size and were hard. Operation was performed six days after trauma. At operation, the left spermatic cord was edematous and was filled with a white, jelly-like substance resembling soft tissues after injection of a local anesthetic. The left epididymis was thickened and purplish red. The left cord was ligated and cut just below the external inguinal ring, and the left testis and cord were removed. Recovery was uneventful.

Epididymitis and orchitis rarely occur after trauma, because of the protection afforded the epididymis and the testis by the anatomic features of the scrotum. Trauma to the scrotum also may result in hydrocele or hematocele, which cannot be distinguished accurately from epididymitis and orchitis. When epididymitis and orchitis are present, infection should be ruled out before a direct cause and effect relationship to trauma can be established and elimination of infection as an etiologic factor may be difficult. When infectious epididymitis and orchitis have occurred and there is a history of trauma, two features may be considered. These are the exact relationship of the trauma, whether direct or indirect, and the pathogenesis of the infection.

URETHRA

Trauma.—Conger⁴⁵ reported 5 cases of war wounds of the urethra. All the patients received initial treatment in the battle area and arrived at the hospital six to eight weeks later. Three of these patients had been struck by machine gun

fire, 2 while lying on the ground, and the third while falling to take cover. The fourth patient had been struck by a rifle bullet while standing erect. The fifth soldier had been bayoneted through the urethra.

The incidence of war injuries to the genitourinary tract among casualties received from the North African theater of war has been low.

Conger stated that urethral injuries should be treated by the accepted principles of urinary diversion and repair of the urethra, as soon as possible. Urinary diversion is necessary to save the life of the patient and should be carried out immediately. Repair of the urethra is imperative to prevent it from healing in a deformed position and to prevent formation of an excessive amount of scar tissue owing to extravasated blood and urine. The urethra should be repaired as soon as the patient's condition warrants.

Injuries of the bulbous urethra should be approached through the perineum directly over the injury. The torn urethra should be sutured over a catheter which will serve to divert the urine while healing occurs.

Injuries of the membranous and prostatic urethra will require suprapubic drainage in addition to repair of the urethra; they should be approached in the same manner that is used for perineal prostatectomy. Sounds passed from both directions will aid in establishing the continuity of the urethra; thereafter a splinting catheter or a Foley bag can be left in the entire canal. If a Foley bag is available, additional approximation can be obtained by tension on the catheter during the period of healing.

If a small prophylactic dose of sulfathiazole (2 Gm. daily) is used, a splinting urethral catheter usually can be left in the urethra without being changed for a period of four to six weeks without causing urethritis.

In cases of impassable stricture of the bulbous and posterior urethra, the continuity of the urethra may be determined by passing sounds from both directions. If the stricture or discontinuity of the urethra is in the membranous or prostatic urethra, a perineal approach should be used.

Calculi.—Beilin and Grueneberg⁴⁶ said that primary urethral calculi occur rarely. As a rule, they are migratory in character, originate in the bladder or the kidney and become arrested in their descent through the urethra. Joly, in a series of 34 cases of urethral calculi observed in a period of ten years, found only 3 cases in which the calculi were probably autochthonous; in the

44. Mason, A., and Reifstein, G. H.: A Case of Epididymo-Orchitis Following Trauma, *J. Urol.* 52: 338-339 (Oct.) 1944.

45. Conger, K.: War Wounds of the Urethra: A Report of Five Cases, *J. Urol.* 52:590-595 (Dec.) 1944.

46. Beilin, L. M., and Grueneberg, J.: Giant Urethral Calculus, *J. Urol.* 52:596-598 (Dec.) 1944.

remaining cases the calculi were definitely migratory. He stated that it is comparatively rare to find that a calculus has formed in the urethra itself, as the necessary conditions are usually wanting. Englisch, in a review of 405 cases of urethral calculi reported in the literature, found 35 instances of autochthonous stones. Urethral calculi are usually small. It is rare to find one larger than an almond. The majority are the size of an orange seed, although exceedingly large stones, weighing more than 100 Gm., have been reported occasionally. Probably the largest was found in a case reported by Benoit and cited by Englisch; It weighed 1,050 Gm.

Beilim and Grueneberg reported a case of giant urethral calculus. The patient was a man aged 33 years, who had hematuria and dysuria. In the midline of the perineum there was a well defined bulge, about the size of a small hen's egg, which was hard and fixed to the urethra. A metal bougie was passed into the urethra and elicited a characteristic grating sound. Suprapubic cystostomy was performed. An attempt was made to remove the stone through the bladder, but the stone was impacted so tightly that it could not be dislodged. A midline incision was then made in the perineum over the calculus, and it was finally removed by external urethrotomy. The stone weighed 330 grains (21.4 Gm.); it was 6 cm. long and 8.6 cm. in diameter.

PENIS

Phimosis.—Taylor⁴⁷ reported 42 cases of infected phimosis in which immediate operation, usually circumcision, was performed. In no case was there extension of chancroidal or other infection along the entire suture line. Healing occurred by primary intention in 9 cases. Satisfactory healing occurred in 18 cases; some infection of the suture line occurred in 11 cases, and healing was slow in 4 cases. In most cases healing was complicated by ulcers on the glans penis or mucous membrane or on both structures. The average stay in the hospital was ten and two-tenths days.

Taylor concluded that in cases of phimosis with swelling of the prepuce or ulceration beneath it immediate circumcision is the treatment of choice. At operation, after complete exposure, cauterization of ulcers with pure phenol should be done carefully. The acid should not be neutralized. Incisions should be planned to remove ulcers if possible. If this is not possible, cauterized ulcers can be boldly bisected and sutures inserted

through them. Hemostasis must be employed with care, and sutures should be inserted only after thorough disinfection and change of instruments and drapes. Vigorous treatment with sulfonamide compounds and neoarsphenamine should be instituted at once. The prepuce should be slit dorsally in cases of gangrenous infection of the prepuce and in cases in which circumcision is definitely contraindicated.

HERMAPHRODITISM

McKenna and Kiefer⁴⁸ reported 2 cases of true hermaphroditism. A child aged 13 years had an ovotestis in the scrotum on the right side and an ovary in the inguinal canal on the left side. There was a rudimentary vagina opening into the urethra, and pronounced hypospadias was present. Another child, aged 3 years, had a testis in the scrotum on the right side and on the left side an abdominal ovary with a left tube and a rudimentary vagina opening into the urethra. Hypospadias also was present. The second case is one of true lateral hermaphroditism; so was the first case except for a small nodule of ovarian tissue attached to the testis. In each case, the ovary was removed and the patient left the hospital with the testis as the only sex gland remaining.

URINARY INFECTION

Briggs⁴⁹ stated that sterile pyuria is a definite clinical entity, simulating renal and vesical tuberculosis. Sterile pyuria is probably caused by an organism of the coccus group, difficult to grow and hard to find in stained smears. The disease is probably not due to a virus, because virus diseases do not respond to the arsenicals. It is seldom cured by the urinary antiseptics, including the sulfonamide drugs usually employed in cases of renal and vesical infection. It responds, sometimes in a spectacular manner, to the arsenicals.

CHEMOTHERAPY

Exley⁵⁰ considered treatment of sulfonamide-resistant gonorrhea with penicillin. Two hundred and fifty-one patients with sulfonamide-resistant gonorrhea were treated with various amounts of penicillin. The doses varied from 41,300 to 125,000 Oxford units, and the preparation was administered by intramuscular injection.

48. McKenna, C. M., and Kiefer, J. H.: Two Cases of True Hermaphroditism, *J. Urol.* 52:464-469 (Nov.) 1944.

49. Briggs, W. T.: Sterile Pyuria, *J. Urol.* 52:283-287 (Oct.) 1944.

50. Exley, M.: Penicillin Treatment of Sulfonamide-Resistant Gonorrhea with Results of Multiple and the Single Injection Methods, *J. Urol.* 52:626-630 (Dec.) 1944.

47. Taylor, H. B.: Immediate Circumcision for Infected Phimosis: Report of Forty-Two Cases, *J. Urol.* 52:615-619 (Dec.) 1944.

The results of a single injection are dramatic. The amount of penicillin used should be at least 30,000 Oxford units. The absorption-elimination time is short, and this method may later be found more efficacious for previously untreated gonorrheal urethritis. Excessive dilution is frowned on for the intramuscular treatment. This not only causes needless pain at the site of injection but also causes more rapid absorption.

Toxic manifestations occurred in only 5 cases. In all these cases the reactions were transient and minimal. In 77 per cent of the cases subsequent examination failed to disclose the *Neisseria gonorrhea*. The average time required for the cultures to become sterile in all groups was twenty-one and one-tenth hours.

Exley is inclined toward the multiple injection treatment, his preference being either two injections of 50,000 Oxford units for a total of 100,000 Oxford units, or five injections for a total of 80,000 Oxford units. The total dose of penicillin has been reduced. The total period of treatment has been reduced by the multiple injection method. From the observations made, it does not seem desirable or expedient at this time to recommend the one day ambulatory treatment until further clinical studies have been made.

Bosworth, Riba and Schmidlapp,⁵¹ after reviewing 233 cases of sulfonamide-resistant gonorrhea, concluded that 50,000 units of penicillin is an insufficient dose to clear the average gonorrheal infection in human beings and that it results in failures in 23 per cent of cases. A high incidence of positive and doubtful smears occurs during the first fourteen days after treatment, but they do not indicate success or failure. Positive smears and cultures usually suggest failure to cure. Retreatment with 100,000 units will produce satisfactory results in the majority of cases.

Hyperpyrexia and intravenous administration of penicillin will clear 30 per cent of the apparently penicillin-resistant gonorrheal infections. With an increase in the supply of penicillin larger doses may be indicated during fever treatment.

One hundred and sixty thousand units of penicillin administered intramuscularly will result in the highest percentage (98 per cent) of clinical cures in the present day treatment of sulfonamide-resistant gonorrheal infection. Patients with complications should have correspondingly larger doses.

Penicillin is an excellent bacteriostatic in cases of gonorrhea. The clinical cure occurs as a result

of the host's defensive mechanism, provided it is not disturbed by "too much interference."

Helmholz and Sung⁵² reported a detailed study of the bactericidal action of penicillin on the bacterial flora commonly encountered in infections of the urinary tract. Thirty strains of *Streptococcus faecalis*, thirty-nine strains of *Escherichia coli*, thirteen strains of *Proteus ammoniae*, eighteen strains of *Aerobacter aerogenes*, three strains of *Pseudomonas aeruginosa* and eleven strains of *Staphylococcus aureus*, all originally isolated from the urine of patients with various infections of the urinary passages, were employed in the experiments. The following conclusions were drawn: In cases of *Str. faecalis* infection, a concentration of 3 Oxford units of penicillin per cubic centimeter of urine is bactericidal. For *P. ammoniae* 8 units per cubic centimeter of urine is the minimal bactericidal concentration of penicillin. For *Esch. coli* there seems to be a line of demarcation between the resistant and the susceptible strains at a level of 30 Oxford units of penicillin per cubic centimeter of urine. *A. aerogenes* and *Ps. aeruginosa* are strongly resistant to the action of penicillin.

Staph. aureus has served satisfactorily in this investigation as a control. The growth of this organism itself is inhibited at a concentration of 0.033 Oxford unit of penicillin per cubic centimeter of urine.

The bactericidal action of penicillin at the low level of its concentration in urine presents therapeutic possibilities for the treatment of infections due to *Staph. aureus*, *Str. faecalis* and *P. ammoniae*. The resistance of *Esch. coli*, *A. aerogenes* and *Ps. aeruginosa* to penicillin practically rules it out as a means of treating infection of the urinary tract due to these organisms.

Vilter and Blankenhorn⁵³ considered toxic reactions to the newer sulfonamide compounds. Toxic reactions occurred in 116 of 1,936 cases, an incidence of 6 per cent. These reactions were usually of such severity as to compel arrest of treatment. Occasionally, treatment could be resumed by changing to another drug. This could be done oftenest by changing from sulfathiazole to sulfadiazine.

Death was ascribed mainly to toxic effects in 4 cases (0.2 per cent), and death in 5 cases was

52. Helmholz, H. F., and Sung, C.: Bactericidal Action of Penicillin on Bacteria Commonly Present in Infections of Urinary Tract, with Especial Reference to *Streptococcus Faecalis*, *Am. J. Dis. Child.* 68:236-242 (Oct.) 1944.

53. Vilter, C. F., and Blankenhorn, M. A.: The Toxic Reactions of the Newer Sulfonamides, *J. A. M. A.* 126:691-694 (Nov. 11) 1944.

51. Bosworth, N. L.; Riba, L. W., and Schmidlapp, C. J.: Two Hundred and Thirty-Three Cases of Sulfonamide-Resistant Gonorrhea Treated with 50,000 Units of Penicillin, *J. Urol.* 52:631-639 (Dec.) 1944.

certainly hastened by drug intoxication. All fatal toxic reactions were mainly renal and resulted in uremia.

In no instance was blockage of the pelvis or ureter thought to be the cause of death. There was no correlation of the milder forms of intoxication and the more severe or lethal reactions. There are no premonitory signs of renal intoxication. Signs of mild disease of the renal pelvis are microscopic hematuria, oliguria, incontinence, pain and increased concentration of blood urea. If these signs are observed, treatment with sulfonamide compounds should either be stopped or be continued with great care, lest nephrosis occur. The use of alkali and water usually corrects mild symptoms. By the time classic symptoms of uremia appeared, no form of treatment was effective. In this series of cases, blockage of the renal tubule was considered the cause of death; hence, ureteral catheterization was not helpful. In disease of the tubules, symptoms may be absent until the disease is well established and its course irreversible.

Crabtree⁵⁴ stated that the sulfonamide drugs have greatly modified for the better the management of pyelonephritis in pregnancy. Sufficient experience has been accumulated to indicate that the beneficial effects of these drugs in relieving symptoms can be expected in almost all cases, whether or not cure of the patient is accomplished. In a high percentage of patients the urine is rendered sterile.

Among the uncured patients there are some in whom persisting infection has produced extensive damage to the efferent channels or can be expected to injure the renal cortex.

There are two major defects in obstetric practice in relation to pyelonephritis. One is failure to investigate urologically those patients who do not obtain cure through sulfonamide therapy. The other is the fact that many women are left after obstetric care with infection of the urinary tract, and in subsequent years, through long-continued or repeated acute injury, preventable gross damage to the urinary tract results.

Greenhill,⁵⁵ in discussing Crabtree's article on the use of sulfonamide compounds in the treatment of pyelonephritis of pregnancy, stated that the word "pyelitis" is commonly used for the subject under consideration but there is damage to the kidney in most cases; hence the correct term is "pyelonephritis." Likewise, the ureter

is generally involved; and so there are really pyelonephritis and ureteritis. There is a tendency for so-called cured or relieved pyelonephritis to flare up during the puerperium in at least half the cases. If the infection of the urinary tract is present longer than three months after delivery, it is almost certain that a gross pathologic condition is present, and a complete study of the urinary tract must be made. Even if the infection is cleared up, a complete study of the urinary apparatus should be made before another pregnancy is planned, because a woman who has had pyelonephritis in one pregnancy has about 1 chance in 4 of having this complication in a subsequent pregnancy. Contrast this with the usual incidence of pyelonephritis in pregnancy, 1 in 50 cases. If another pregnancy begins before the infection of the urinary tract is cleared up, the chances of recurrence are 1 in 2. Many women have permanent defects, such as hydronephrosis and hydro-ureter, after a single attack of pyelonephritis. The treatment of pyelonephritis by means of the sulfonamide compounds is now relatively simple, but one must be careful in evaluating the results. Anemia must be overcome; constipation must be avoided; the Fowler position should be used for proper drainage; fluids should be forced, and sedatives should be given. The patient must be treated in the same way as before sulfonamide compounds came into use. The treatment with sulfonamide compounds has no bad effect on the babies, and by means of this therapy nearly all patients can be carried to term. There is now rarely any necessity to employ ureteral catheterization or to empty the uterus because of pyelonephritis, but it must be remembered that the sulfonamide compounds will not cure all patients who have pyelonephritis; hence, in an occasional case, pregnancy may have to be terminated. It is difficult to prevent the first attack of pyelonephritis except by removing foci of infection. Once a woman has had pyelonephritis, not only must she be carefully checked for a long time following the first attack but also her urinary tract must be studied before each new pregnancy. Prophylactic therapy with the sulfonamide drugs in successive pregnancies will certainly reduce the incidence of recurrence of severe pyelonephritis and produce rapid cures, because the patient can be treated early.

Corbus,⁵⁶ in discussing Crabtree's article on the use of sulfonamide compounds for pyelonephritis of pregnancy, stated that termination of pregnancy does not cure the infection of

54. Crabtree, E. G.: The Use of the Sulfonamides in Pyelonephritis in Pregnancy, *J. A. M. A.* 126:810-814 (Nov. 25) 1944.

55. Greenhill, J. P., in discussion on Crabtree,⁵⁴ p. 813.

56. Corbus, B. C., in discussion on Crabtree,⁵⁴ 813-814.

urinary tract. The patients should be studied and treated after the pregnancy ends, in order to restore adequate urinary drainage if possible. As a pathologic condition of the urinary tract was shown to exist after termination of pregnancy in all cases studied, it seemed reasonable to assume that obstructive pathologic changes may have been present before the pregnancy began. There is no doubt that the pressure of the fetal head and the hormonal influence which causes dilatation of the ureter, with lessened peristaltic action, accompanied with urinary stasis, may be contributing factors in pyelitis; however, if these were the significant factors, more pregnant women would have complicating pyelitis. Corbus thinks that one can consider that pyelitis of pregnancy is a clinical exacerbation of a previous latent chronic infection of the urinary tract and, in demonstrating this, the modern conception of possible pathologic changes in the vesical neck should not be forgotten. Every one is aware of the value of the sulfonamide drugs for nonpregnant women; at the same time it must be taken into account that these drugs are dangerous and that their administration should be well supervised. The use of drug therapy during an attack of pyelitis of pregnancy by no means replaces complete urologic study after the pregnancy has terminated.

Kobak,⁵⁷ in discussing Crabtree's article on the use of sulfonamide compounds in the treatment of pyelonephritis in pregnancy, stated that all cases of pyelitis occurring in the obstetric services of Cook County Hospital were studied during a period of twenty-one months and the findings were published. The material consisted of 143 cases, an incidence of 1.63 per cent. Ninety-five patients had pyelitis ante partum and 48 during the puerperium. It was necessary to interrupt the pregnancy in only 1 case, and there were no deaths in the series of cases studied. Subsequent to this report, there were 3 deaths. All 3 patients who died had retention of nitrogenous products. In more than a third of the cases of puerperal pyelitis there were etiologic factors that one frequently observes in cases of puerperal sepsis. Thus, there were prolonged labors, difficult forceps deliveries and cesarean sections that were not elective. Many of the patients who had pyelitis also had concomitant puerperal sepsis. In view of the anatomic relation of the urologic and genital systems, this fact is not surprising.

Jensen and Fox⁵⁸ considered the treatment of renal obstruction resulting from sulfadiazine and

sulfamerazine and reported 3 cases. They stated that precipitation of sulfadiazine within the kidneys and ureters is more common than is generally recognized. Precipitation can best be prevented by maintaining an alkaline urine and forcing ingestion of fluids. In the majority of cases the administration of 1 Gm. of sodium bicarbonate every four hours will neutralize the acidity of the sulfonamide drug but will not overcome the usual acidity of the urine. The p_H of the urine must be followed when 3 Gm. or more of sulfadiazine, sulfathiazole or sulfamerazine is being administered daily.

When urinary obstruction occurs, whether partial or complete, the patient should be hospitalized immediately. If oliguria exists, sodium bicarbonate should be administered orally, intravenously and, if necessary, rectally, to produce systemic alkalization and dissolve the crystals. If anuria exists, repeated pelvic and ureteral lavage with a warm 10 per cent solution of sodium bicarbonate will dissolve crystals within the pelves and ureters. Systemic alkalization with sodium bicarbonate should follow. Previous failures with systemic alkalization are attributable to use of quantities of sodium bicarbonate insufficient to produce a strongly alkaline urine. Isotonic solution of sodium lactate (1.75 per cent solution—35 Gm. of the 50 per cent syrup in a liter) offers the advantage of palatability for oral use and ease of sterilization by autoclaving for parenteral administration. The urine can be made alkaline with 2 or more liters of this solution.

Sulfamerazine is a relatively new drug, and to Jensen and Fox's knowledge this is the first report of a case in which renal obstruction was attributed to use of this drug. Although the solubility of this drug is slightly higher than that of sulfadiazine in acid urine, the difference is not sufficient to keep in solution the concentration of drug excreted in the urine during routine therapy. In urine of a p_H of more than 7.5, sulfamerazine is less soluble than sulfadiazine.

TUMORS OF THE UROGENITAL TRACT OF YOUNG PERSONS

Bandler and Roen⁵⁹ stated that the most frequent tumor of the urogenital tract in children is Wilms's tumor of the kidney. Diagnosis can be made in most instances by urographic measures.

58. Jensen, O. J., and Fox, C. L.: The Treatment of Renal Obstruction Resulting from Sulfadiazine and Sulfamerazine, *J. Urol.* 52:346-352 (Oct.) 1944.

59. Bandler, C. G., and Roen, P. R.: Tumors of the Urogenital Tract in the Young, *Am. J. Surg.* 65: 306-314 (Sept.) 1944.

57. Kobak, A. J., in discussion on Crabtree,⁵⁴ p. 814.

Preoperative and postoperative roentgen therapy should be given. The transperitoneal approach for removal of the kidney should be employed.

Less frequent in occurrence are tumors of the adrenal gland, the bladder, the prostate and the testis, but the possibility of their existence, even in very young persons, must be emphasized and thorough search made for signs of these highly malignant growths.

Early diagnosis of malignant disease of the genitourinary tract in children is essential to successful therapy. In all cases one should employ both operation and roentgen therapy. Radiation therapy should not be employed alone except in cases in which widespread metastasis is present.

URINARY RETENTION AFTER OPERATIONS ON THE RECTUM AND THE SIGMOID

Emmett and Cristol⁶⁰ reported a group of cases in which transurethral resection was performed after removal of the rectum or the sigmoid for carcinoma. The site of the malignant growth varied from 2 to 12 cm. above the anal margin. The age of the patients varied from 37 to 75 years, but the majority (29 of the patients were more than 50 years of age, while all but 1 were more than 40 years of age). All of the patients were in the age of prostatism.

In 24 of the cases no urinary symptoms of any kind were elicited in the history prior to the intestinal operation. In only 4 of the 33 cases did the symptoms seem to justify determination of the residual urine. In 2 cases there was no residual urine, and in the remaining 2 the amounts of residual urine found were 25 and 140 cc. respectively. In 6 cases the prostate gland was reported to be normal in size and consistency; in 5 cases it was enlarged, grade 1 (on a basis of 1 to 4 in which 1 designates the least and 4 the greatest enlargement); in 3 cases it was enlarged to grade 1+, while in 1 other case it was described as enlarged to grade 2.

60. Emmett, J. L., and Cristol, D. S.: Urinary Retention Following Surgical Operation on the Rectum and Sigmoid: Treatment by Transurethral Resection. *J. A. M. A.* 126:1077-1079 (Dec. 23) 1944.

After the operation on the bowel the complications in these cases were similar to cases of urinary retention. Most of the patients were unable to void, but others were able to void small quantities but large quantities of residual urine. Intermittent or indwelling catheterization was necessary in these cases; hence in many cases pyuria developed in spite of urinary sepsis.

In most of these cases conservative measures of various types were employed in an attempt to stimulate the bladder. Most of the patients were given a period of more than three weeks for the bladder to recover. Almost all patients in this group were allowed more than two months.

The cystoscopic findings in these cases were interesting. In the majority of cases the most prominent finding was a rather deep "sagging" type of bladder, with the appearance that the supporting structure of the region of the base of the bladder was gone. It has been Emmett and Cristol's feeling that this lack of support rather than the disturbance of the nerve supply of the bladder is one of the greatest factors in the vesical atony.

An accurate cystoscopic evaluation of the vesical neck is extremely important. In the 33 cases under discussion, cystoscopy was performed prior to resection, while in 16 cases it was performed only at the time of resection. From the cystoscopist's description of the vesical neck one gains the impression that there was no visible evidence of obstruction in 13 cases, a minimal amount of obstruction in 16 cases and a moderate amount of obstruction in only 4 cases. In spite of this the cystoscopic appearance of the vesical neck after transurethral resection was performed on all of these patients. In 17 cases (approximately half) less than 10 Gm. of tissue was removed, while in only 6 cases was it necessary to remove more than 20 Gm.

The results of transurethral resection in these cases have been good. In 30 cases they are regarded as excellent, which means that normal vesical function returned and the residual urine was completely eliminated.

INDEX TO VOLUME 50

- Abbott, W. E.: Metabolic alterations following thermal burns; effect of variations in food intake on nitrogen balance of burned patients, 194
- Abdomen, desmoid tumor, 304
- Abeshouse, B. S.: Malignant renal neoplasms: clinical and pathologic study, 46
- Abnormalities and Deformities: See under names of diseases, organs and regions, as Anus; Bladder; Face; Kidneys; etc.
- Abscess: See under names of organs and regions
- Accidents: See Trauma; etc.
- Acrylic Resin as implant for correction of facial deformities, 233
- Actinomycosis of bladder, 112
- Adams, R.: Postoperative gouty arthritis, 229
- Adams, W. E.: *Some recent accomplishments of thoracic surgery*, 277
- Alcohol, Therapy: See under Anus
- Allen, A. W.: Neckel's diverticulum containing calculi, 286
- Ambulation: See Surgery
- American Academy of Orthopaedic Surgeons, progress in orthopedic surgery for 1943; review prepared by Editorial Board of, 89
- Amputation, apparatus and technic, 89
ligation of femoral vein for chronic occlusive arterial disease; review of 118 ligations, 56
- Amyloidosis of bladder, 112
- Analgesia: See Anesthesia; Pain
- Anesthesia: See also Surgery
blocking of middle cervical and stellate ganglions with descending infiltration anesthesia; technic, accidents and therapeutic indications, 152
Cold: See Cold
continuous spinal anesthesia; observations on 1,200 patients, 130
- Anesthetics: See Anesthesia
- Aneurysm and urinary symptoms, 123
renal, 107
- Anomalies: See under names of diseases, organs and regions
- Antisepsis and Antiseptics: See also under Urinary Tract
prophylaxis of wound infection; studies with reference to soaps and irrigation, 177
- Anuria: See Urine, suppression
- Anus: See also Rectum
congenital malformations of anus and rectum: clinical study, 253
methods for reducing pain following hemorrhoidectomy; technic and results in 72 cases, 293
- Apparatus: See also Instruments
amputations, apparatus and technic, 89
orthopedic, 92
- Appendicitis: See also Appendix
acute, in childhood, 258
- Appendix, Abscess: See Appendicitis
lymphosarcoma primary in; study of 23 cases, 288
- Arms: See Military Medicine
- Arteries: See also Aneurysm; Blood, pressure; etc.
periarterial infiltration in diagnosis and treatment of migraine; experimental and clinical experience with eucupine and procaine hydrochloride, 296
- Arthritis, postoperative gouty arthritis, 229
- Arthrotomies: See Knee
- Atrophy: See under names of organs and regions
- Bacteria, Actinobacilli: See Actinomycosis
- Basedow's Disease: See Goiter, exophthalmic
- Bergman, H. C.: Influence of environmental temperature on shock, 201
- Bladder: See also Urinary Tract
abnormalities; congenital obstruction of vesical neck, 318
actinomycosis of, 112
amyloidosis of, 112
calculi, 315
diverticulum, 110
experience with calculus in north China, 82
Fistula: See Fistula
gumma of, 112
trauma, 111
tumors, 316
xanthic calculus, 112
- Blennorrhagia: See Gonorrhea
- Blood: See also Erythrocytes; Leukocytes
coagulation; thromboplastic reagent; development of more suitable preparation for measuring accelerated clotting tendency and for use following administration of dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]), 137
Iodine studies; analysis of blood iodine in thyroid disease, 207
pressure, high; renal hypertension, 315
proteins; postoperative gouty arthritis, 229
prothrombin; thromboplastic reagent; development of more suitable preparation for measuring accelerated clotting tendency and for use following administration of dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]), 137
transfusion; evaluation of gelatin and pectin solutions as substitutes for plasma in treatment of shock; histologic changes produced in human beings, 34
- Bones: See also under names of bones
Diseases: See Osteomyelitis; etc.
osseous, cartilaginous and mixed tumors of human breast; review of literature, 184
- Brain, convulsive factor in commercial penicillin, 69
- Brambel, C. E.: Thromboplastic reagent; development of more suitable preparation for measuring accelerated clotting tendency and for use following administration of dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]), 137
- Breast, osseous, cartilaginous and mixed tumors of human breast; review of literature, 184
- Bright's Disease: See Nephritis
- Bryson, V.: Topical use of concentrated penicillin in surface-active solution, 219
- Burns, degenerative white blood cell picture as indication of toxemia from burns, 242
influence of environmental temperature on shock, 201
metabolic alterations following thermal burns; effect of variations in food intake on nitrogen balance of burned patients, 194
- Calculi: See under Bladder; Intestines; Kidneys; Urethra; etc.
- Calorimetry: See Metabolism

- Cambel, P.: Chronic thyroiditis and primary thyrotoxicosis (exophthalmic goiter), 125
- Cancer: See Sarcoma; Tumors; and under names of organs and regions, as Kidneys; Prostate; etc.
- Carbuncle, Renal: See Nephritis
- Carpus: See Wrist
- Cartilage, osseous, cartilaginous and mixed tumors of human breast; review of literature, 184
- transplantation of epiphyseal cartilage, 148
- Cerebrum: See Brain
- Chemotherapy, 119, 330. See also Penicillin; Sulfonamides; etc.
- Chest: See Thorax
- Children: See also Infants
- acute appendicitis in childhood, 258
- China and Chinese, experience with calculus of bladder in north China, 82
- Chondrogenesis: See under Cartilage
- Cipolla, A. F.: Masked traumatic rupture of spleen, 87
- Climacteric, male, 123
- Cold: See also Temperature
- anesthesia; amputations, 59
- Coleman, F. P.: Traumatic hemothorax; decortication in treatment of chronic uninfected type, 14
- Colon: See also Intestines; Sigmoid
- cysts of urachus, 174
- Convalescence, protein metabolism during convalescence after trauma; recent studies, 166
- Convulsions, convulsive factor in commercial penicillin, 69
- Cook, E. N.: Review of urologic surgery, 104, 309
- Coumarin, thromboplastic reagent; development of more suitable preparation for measuring accelerated clotting tendency and for use following administration of dicoumarin (3,3'-methylenebis-[4-hydroxycoumarin]), 137
- Cryptorchism: See Testes
- Curtis, G. M.: Blood iodine studies; analysis of blood iodine in thyroid disease, 207
- Cystostomy: See under Bladder
- Cysts: See under names of organs and regions, as Kidneys; Urachus; etc.
- Dandy, W. E.: Ménière's disease in deaf-mute, 74
- Deaf-Mutism, Ménière's disease in deaf-mute, 74
- Deformities: See under names of diseases, organs and regions
- Derhes, V.: Periarterial infiltration in diagnosis and treatment of migraine; experimental and clinical experiences with eucupine and procaine hydrochloride, 296
- Dicoumarin: See Coumarin
- Diet and Dietetics: See also Nutrition
- metabolic alterations following thermal burns; effect of variations in food intake on nitrogen balance of burned patients, 194
- D'Inglanni, V.: Early and late postoperative ambulation; comparative study of 303 cases, 214
- Disk, Intervertebral: See under Spine
- Diverticula: See Bladder; Intestines; etc.
- Dmytryk, E. T.: Congenital malformations of anus and rectum; clinical study, 253
- Donaldson, G. A.: Meckel's diverticulum containing calculi, 286
- Duodenum, Ulcers: See Peptic Ulcer
- Elephantiasis; surgical treatment of lymphedema, 269
- Engelhardt, H.: Periarterial infiltration in diagnosis and treatment of migraine; experimental and clinical experiences with eucupine and procaine hydrochloride, 296
- Enteritis: See Intestines
- Enuresis: See Urination, Incontinence
- Environment, influence of environmental temperature on shock, 201
- Epididymis, malignant tumors, 119
- Epididymitis, traumatic, and orchitis, 329
- Epiphyses, slipping of upper femoral epiphysis; diagnostic and therapeutic considerations, 19
- transplantation of epiphyseal cartilage, 148
- Erythrocytes, count; masked traumatic rupture of spleen, 87
- Eucupine: See Migraine
- Exophthalmos: See Goiter, exophthalmic
- Extremities: See also under names of bones
- Amputation: See Amputation
- ligation of femoral vein for chronic occlusive arterial disease; review of 118 ligations, 56
- Face, acrylic resin as implant for correction of facial deformities, 233
- Femur, Epiphyses: See Epiphyses
- Fertman, M. B.: Blood iodine studies; analysis of blood iodine in thyroid disease, 207
- Ficarra, B. J.: Postoperative gouty arthritis, 229
- Fistula, arteriovenous, between right common iliac artery and inferior vena cava; report of case of its occurrence following operation for ruptured intervertebral disk with cure by operation, 6
- rectourinary, 124
- Food: See Diet and Dietetics; Nutrition
- Foot, transplantation of epiphyseal cartilage, 148
- Foramen, Intervertebral: See under Spine
- Freezing: See Cold
- Funderburk, W. H.: Convulsive factor in commercial penicillin, 69
- Fungi: See Actinomyces; etc.
- Ganglion, Stellate: See Anesthesia
- Gangrene, thromboplastic reagent; development of more suitable preparation for measuring accelerated clotting tendency and for use following administration of dicoumarin (3,3'-methylenebis-[4-hydroxycoumarin]), 137
- Gastrectomy: See under Stomach
- Gastric Ulcer: See Peptic Ulcer
- Gastrointestinal Tract: See Colon; Intestines; Rectum; Stomach; etc.
- Gay, L. C.: Pneumothorax resulting from dissecting gastric ulcer; review of literature and report of case, 301
- Gelatin, evaluation of gelatin and pectin solutions as substitutes for plasma in treatment of shock; histologic changes produced in human beings, 24
- Genitals: See Genitourinary Tract; Urinary Tract; and under names of genitals, as Penis; etc.
- Genitourinary Tract: See also Urinary Tract
- tumors of urogenital tract of young persons, 233
- use of penicillin in genitourinary infections, 119
- Glasser, S. T.: Ligation of femoral vein for chronic occlusive arterial disease; review of 118 ligations, 56
- Globulin in Blood: See Blood, proteins
- Goiter: See also Thyroid
- exophthalmic; chronic thyroiditis and primary thyrotoxicosis (exophthalmic goiter), 125

- Gonorrhea, penicillin treatment of, 119
treatment of sulfonamide-resistant gonorrhea with penicillin, 330
- Gout, postoperative gouty arthritis, 229
- Grace, E. J.: Topical use of concentrated penicillin in surface-active solution, 219
- Grafts: See Cartilage
- Graves' Disease: See Goiter, exophthalmic
- Green, C. C.: Desmold tumor, 304
- Green, W. T.: Slipping of upper femoral epiphysis: diagnostic and therapeutic considerations, 19
- Gürkan, K. I.: Chronic thyroiditis and primary thyrotoxicosis (exophthalmic goiter), 125
- Gumma: See under Bladder
- Gutierrez, R.: Review of urologic surgery, 104, 309
- Headache: See Migraine
- Heat: See Temperature
- Heller, C. G.: Metabolic alterations following thermal burns; effect of variations in food intake on nitrogen balance of burned patients, 194
- Hematoma, syndrome of trauma to psoas muscle, 77
- Hemorrhoids, methods for reducing pain following hemorrhoidectomy; technique and results in 72 cases, 293
- Hemothorax, traumatic; decortication in treatment of chronic uninfected type, 14
- Henry, M. G.: Anomalous fusion of scapula and greater multangular bone, 240
- Hepner, A. B.: Review of urologic surgery, 104, 309
- Hermaphroditism, 122, 330
- Hinman, F.: Review of urologic surgery, 104, 309
- Hirschfeld, J. W.: Metabolic alterations following thermal burns; effect of variations in food intake on nitrogen balance of burned patients, 194
- Howard, J. E.: Protein metabolism during convalescence after trauma; recent studies, 166
- Hudson, P. B.: Pneumothorax resulting from dissecting gastric ulcer; review of literature and report of case, 301
- Hydatid of Morgagni: See Testes
- Hydronephrosis, 312
- Hypertension: See Blood pressure, high
- Hypoprothrombinemia: See Blood, prothrombin
- Ileum: See Intestines
- Ileus: See Intestines
- Incontinence: See Urination, incontinence
- Infants, newborn; congenital malformations of anus and rectum; clinical study, 253
- Infection: See also Wounds; and under names of bacteria
topical use of concentrated penicillin in surface-active solution, 219
- Injuries: See Trauma; and under diseases, organs and regions, as Bladder; Penis; Urethra; etc.
- Instruments: See also Apparatus
new surgical, 94
- Intervertebral Disk: See Spine, intervertebral disk
- Intestines: See also Colon; Rectum; Sigmoid
Intussusception: See Intussusception
Meckel's diverticulum containing calculi, 286
Ulcers: See Peptic Ulcer
- Intussusception, unusual ileocecal intussusception, 307
- Iodine in Blood: See Blood, iodine
- Irrigation, prophylaxis of wound infection; studies with reference to soaps and irrigation, 177
- Jackle, R. F.: Internal derangements of knee joint, 271
- Jejunum: See Intestines
- Ulcers: See Peptic Ulcer
- Johnson, H. C.: Convulsive factor in commercial penicillin, 69
- Joints: See under names of individual joints, as Knee; etc.
- Kidneys: See also Urinary Tract
anomalies, 104, 309
calculi, 106
Diseases: See Hydronephrosis; Nephritis
malignant renal neoplasms; clinical and pathologic study, 46
operations, 313
ptosis, 107
renal hypertension, 315
subcapsular extravasation, 107
trauma, 107
tuberculosis, 312
tumors, 105, 311
Wilms's tumor of, 333
- Knee; internal derangements of knee joint, 271
- Knox, G.: Lymphosarcoma primary in appendix; study of 23 cases, 288
- Kozoll, D. D.: Evaluation of gelatin and pectin solutions as substitutes for plasma in treatment of shock; histologic changes produced in human beings, 34
- Lee, T. F.: Use of omentum to close perforations of stomach, 171
- Legs: See also Extremities; Foot: Knee; and under names of bones
Amputation: See Amputation
- Leukocytes, degenerative white blood cell picture as indication of toxemia from burns, 242
- von Lichtenberg, A.: Review of urologic surgery, 104, 309
- Ligaments: See Knee
Triangular: See Wrist
- Linton, R. R.: Arteriovenous fistula between right common iliac artery and inferior vena cava; report of case of its occurrence following operation for ruptured intervertebral disk with cure by operation, 6
- Livingstone, H.: Continuous spinal anesthesia; observations on 1,200 patients, 130
- Lungs: See Respiration; Thorax; etc.
- Lymph Nodes: See Lymphosarcoma
- Lymphedema: See Elephantiasis
- Lymphosarcoma primary in appendix; study of 23 cases, 288
- Mammary Gland: See Breast
- Marlin, R. C.: Continuous spinal anesthesia; observations on 1,200 patients, 130
- Meckel's Diverticula: See under Intestines
- Medicine, Military: See Military Medicine
- Melick, D. W.: Subtotal gastrectomy, 223
- Ménière's Disease: See Vertigo, aurai
- Metabolism, blood iodine studies; analysis of blood iodine in thyroid disease, 207
metabolic alterations following thermal burns; effect of variations in food intake on nitrogen balance of burned patients, 194
- 3,3'-Methylene-Bis-(4-Hydroxycoumarin): See Coumarin
- Meyer, F.: Metabolic alterations following thermal burns; effect of variations in food intake on nitrogen balance of burned patients, 194

- Meyer, K. A.: Evaluation of gelatin and pectin solutions as substitutes for plasma in treatment of shock; histologic changes produced in human beings, 34
- Michelson, E.: Syndrome of trauma to psoas muscle, 77
- Micturition: See Urination
- Migraine, periarterial infiltration in diagnosis and treatment; experimental and clinical experiences with eucupine and procaine hydrochloride, 296
- Military Medicine, internal derangements of knee joint, 271
- testicular tumors, 63
- Multangular Bone: See Wrist
- Muscles, syndrome of trauma to psoas muscle, 77
- Narat, J. K.: Masked traumatic rupture of spleen, 87
- Narcosis: See Anesthesia
- Navicular Bone: See Scaphoid Bone, Carpal
- Nephrectomy: See under Kidneys
- Nephritis, surgical aspect of, 314
- Nerves, Blocking: See under Anesthesia
- early repair of neural wounds with penicillin therapy, 67
- Nervous System: See Brain; Nerves; etc.
- Newborn Infants: See Infants, newborn
- Newman, H. E.: Pneumothorax resulting from dissecting gastric ulcer; review of literature and report of case, 301
- Nipple: See Breast
- Nitrogen, metabolic alterations following thermal burns; effect of variations in food intake on nitrogen balance of burned patients, 194
- Norcross, N. C.: Early repair of neural wounds with penicillin therapy, 67
- Nucleus Pulposus: See Spine, Intervertebral disk
- Nutrition: See also Diet and Dietetics; etc.
- experience with calculus of bladder in north China, 82
- Obl, R.: Metabolic alterations following thermal burns; effect of variations in food intake on nitrogen balance of burned patients, 194
- O'Connor, V. J.: Review of urologic surgery, 104, 309
- Oliguria: See Urine, suppression
- Omentum, use to close perforations of stomach, 171
- Operating Rooms: See Surgery
- Orchitis: See Testes
- Orthopedic Surgery, progress for 1943; review prepared by Editorial Board of American Academy of Orthopaedic Surgeons, 89
- Osteomyelitis, topical use of concentrated penicillin in surface-active solution, 219
- Owings, J. C.: Methods for reducing pain following hemorrhoidectomy; technic and results in 72 cases, 293
- Oxygen: See Respiration
- Pain, methods for reducing pain following hemorrhoidectomy; technic and results in 72 cases, 293
- Patzner, R.: Periarterial infiltration in diagnosis and treatment of migraine; experimental and clinical experiences with eucupine and procaine hydrochloride, 296
- Paul, M.: Unusual ileocecal intussusception, 307
- Pectin, evaluation of gelatin and pectin solutions as substitutes for plasma in treatment of shock; histologic changes produced in human beings, 34
- Penhale, K. W.: Acrylic resin as implant for correction of facial deformities, 233
- Penicillin, commercial, convulsive factor in, 69
- topical use of concentrated penicillin in surface-active solution, 219
- Therapy: See Gonorrhea; Nerves; etc.
- Penis, trauma, 119
- Peptic Ulcer, pneumothorax resulting from dissecting gastric ulcer; review of literature and report of case, 301
- Peterson, L. W.: Propylaxis of wound infection; studies with reference to soaps and irrigation, 177
- Phimosis, 330
- Pilling, M. A.: Metabolic alterations following thermal burns; effect of variations in food intake on nitrogen balance of burned patients, 194
- Plastic Surgery: See under Face
- Plastics: See Acrylic Resin
- Pneumothorax resulting from dissecting gastric ulcer; review of literature and report of case, 301
- Popper, H.: Evaluation of gelatin and pectin solutions as substitutes for plasma in treatment of shock; histologic changes produced in human beings, 34
- Prepuce: See Penis; Phimosis
- Price, P. B.: Experience with calculus of bladder in north China, 82
- Use of omentum to close perforations of stomach, 171
- Prinzmetal, M.: Influence of environmental temperature on shock, 201
- Procaine Hydrochloride: See Anesthesia; Migraine
- Prostate, carcinoma, 115, 313
- operations on, 113, 327
- Prostatectomy: See under Prostate
- Proteins, in Blood: See Blood, proteins
- metabolic alterations following thermal burns; effect of variations in food intake on nitrogen balance of burned patients, 194
- metabolism during convalescence after trauma; recent studies, 166
- Prothrombin: See Blood, coagulation
- Prosis: See under Kidneys
- Pyuria: See Urinary Tract, Infections
- Ransohoff, J. L.: Surgical treatment of lymphedema, 269
- Recruits: See Military Medicine
- Rectum, congenital malformations of anus and rectum; clinical study, 233
- urinary retention after operations on rectum and sigmoid, 334
- Refrigeration: See Cold
- Research, 97
- Respiration, traumatic hemothorax; decortication in treatment of chronic uninfected type, 14
- Richards, A. J.: Metabolic alterations following thermal burns; effect of variations in food intake on nitrogen balance of burned patients, 194
- Röntgen Rays: See under names of organs, regions and diseases
- Rottino, A.: Osseous, cartilaginous and mixed tumors of human breast; review of literature, 184
- Sarcoma: See also Lymphosarcoma; Tumors; etc.
- osseous, cartilaginous and mixed tumors of human breast; review of literature, 184

- Sawyer, C. F.: Cysts of urachus, 174
- Scaphoid Bone, Carpal; anomalous fusion of scaphoid and greater multangular bone, 240
- Schmidt, E. R.: Subtotal gastrectomy, 223
- Scholl, A. J.: Review of urologic surgery, 104, 309
- Scott, H. W., Jr.: Acute appendicitis in childhood, 258
- Sex, Intergrades: See Hermaphroditism
- Shock, clinical, orientation to mechanisms of, 1
evaluation of gelatin and pectin solutions as substitutes for plasma in treatment of shock; histologic changes produced in human beings, 34
influence of environmental temperature on, 201
- Sigmoid: See also Colon; Intestines
urinary retention after operations on rectum and sigmoid, 334
- Scaps, prophylaxis of wound infection; studies with reference to soaps and irrigation, 177
- de Sousa Perelra, A.: Blocking of middle cervical and stellate ganglions with descending infiltration anesthesia; technique, accidents and therapeutic indications, 152
- Spermatic Cord, tumors, 119
- Spine, intervertebral disk; arteriovenous fistula between right common iliac artery and inferior vena cava; report of case of its occurrence following operation for ruptured intervertebral disk with cure by operation, 6
- Spleen, masked traumatic rupture of, 87
- Stead, E. A., Jr.: Orientation to mechanisms of clinical shock, 1
- Steigmann, F.: Evaluation of gelatin and pectin solutions as substitutes for plasma in treatment of shock; histologic changes produced in human beings, 34
- Steindler, A.: Research, 97
- Stomach, subtotal gastrectomy, 223
Ulcers: See Peptic Ulcer
use of omentum to close perforations of, 171
- Sulfonamides and anuria, 120
- Surgery: See also Apparatus; Instruments; Wounds; etc.
early and late postoperative ambulation; comparative study of 303 cases, 214
postoperative gouty arthritis, 229
thromboplastic reagent; development of more suitable preparation for measuring accelerated clotting tendency and for use following administration of dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]), 137
- Syphilis: See under names of organs and regions
- Temperature: See also Cold
influence of environmental temperature on shock, 201
- Testes: See also Epididymis; Epididymitis
cryptorchism, 327
rupture of, 328
traumatic epididymitis and orchitis, 329
tumors, 63, 118, 327
- Thompson, G. J.: Review of urologic surgery, 104, 309
- Thorax, surgery, some recent accomplishments of, 277
traumatic hemothorax; decortication in treatment of chronic uninfected type, 14
- Thrombophlebitis, thromboplastic reagent; development of more suitable preparation for measuring accelerated clotting tendency and for use following administration of dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]), 137
- Thyroid, blood iodine studies; analysis of blood iodine in thyroid disease, 207
chronic thyroiditis and primary thyrotoxicosis (exophthalmic goiter), 125
- Thyroiditis: See under Thyroid
- Thyrotoxicosis: See Goiter
- Toxemia, degenerative white blood cell picture as indication of toxemia from burns, 242
- Transplantation: See Cartilage; Ureters; etc.
- Trauma: See also Hemothorax; Shock; etc.
protein metabolism during convalescence after trauma; recent studies, 166
masked traumatic rupture of spleen, 87
thromboplastic reagent; development of more suitable preparation for measuring accelerated clotting tendency and for use following administration of dicoumarin (3,3'-methylene-bis-[4-hydroxycoumarin]), 137
- Tuberculosis: See under names of diseases, organs and regions, as Kidneys; etc.
- Tumors: See also Lymphosarcoma; Sarcoma; and under names of organs and regions, as Bladder; Breast; Kidneys; Testes; Ureters; etc.
desmoid, 304
osseous, cartilaginous and mixed tumors of human breast; review of literature, 184
Wilms: See under Kidneys
- Ulcers, Peptic: See Peptic Ulcer
- Urachus, cysts of, 174
- Ureterotomy: See under Ureters
- Ureters: See also Urinary Tract
intubated ureterotomy, 109
transplantation, 108
tumors, 315
- Urethra, calculus, 329
repair, 116
trauma, 329
- Urinary Tract: See also Genitourinary Tract; Kidneys; Ureters; etc.
aneurysm and urinary symptoms, 123
infections, 122, 330
roentgenologic aspects of urology, 124
- Urination, incontinence; stress incontinence, 113
urinary retention after operations on rectum and sigmoid, 334
- Urine: See also Urination
suppression; sulfonamide compounds and anuria, 120
- Urologic surgery, review of, 104, 309
- Van Duyn, J., II: Degenerative white blood cell picture as indication of toxemia from burns, 242
- Vasomotor System: See Arteries; Blood pressure; Veins
- Veins: See also Thrombophlebitis
ligation of femoral vein for chronic occlusive arterial disease; review of 118 ligations, 56
Pressure: See Blood pressure
- Venous Pressure: See Blood pressure
- Vermooten, V.: Testicular tumors, 63
- Vertebrae: See Spine
- Vertigo, aural; Ménière's disease in deaf-mute, 74
- Verumontanum: See Urethra
- Vincenzi, A. L.: Masked traumatic rupture of spleen, 87
- Vitamins, K: See Blood, coagulation
- Volk, B. W.: Evaluation of gelatin and pectin solutions as substitutes for plasma in treatment of shock; histologic changes produced in human beings, 34
- Walker, A. E.: Convulsive factor in commercial penicillin, 69
- War: See Military Medicine; Wounds; etc.

- Ware, P. F.: Acute appendicitis in childhood, 259
- Warren, J. V.: Orientation to mechanisms of clinical shock, 1
- Weinberg, T.: Malignant renal neoplasms; clinical and pathologic study, 46
- Wellman, V.: Continuous spinal anesthesia; observations on 1,200 patients, 130
- Wenger, H. L.: Transplantation of epiphyseal cartilage, 149
- White, J. W.: Amputations, apparatus and technic, 89
- White, P. D.: Arteriovenous fistula between right common iliac artery and inferior vena cava; report of case of its occurrence following operation for ruptured intervertebral disk with cure by operation, 6
- Wilddolz, E.: Review of urologic surgery, 104, 309
- Williams, H. H.: Metabolic alterations following thermal burns; effect of variations in food intake on nitrogen balance of burned patients, 194
- Wilson, K.: Osseous, cartilaginous and mixed tumors of human breast; review of literature, 184
- Wilms Tumor: See under Kidneys
- Wounds: See also Military Medicine
Prophylaxis of wound infection; studies with reference to soaps and irrigation, 177
traumatic hemothorax; decortication in treatment of chronic uninfected type, 14
- Wrist: See also Scaphoid Bone, Carpal
anomalous fusion of scaphoid and greater multangular bone, 240

